ASSESSMENT AND ACCESS TO RENAL TRANSPLANTATION FOR RENAL FAILURE PATIENTS

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One's mind, once stretched by a new idea, never regains its original dimensions.

Oliver Wendell Holmes (1809-1894)

Author's statement

The work contained in this thesis was carried out during my appointment as a Research Registrar in the Transplant Unit, at the Royal Infirmary of Edinburgh. The studies were composed and designed by myself with advice from Mr. John Forsythe.

All studies were performed by myself with respect to data collection and analysis. The baseline sociodemographic data as well as dialysis and transplant data were retrieved from the Scottish Renal Registry and United Kingdom Transplant databases, while the clinical data were collected by myself in each of the four transplant centres in Scotland.

Statistical analysis of the results were performed using SPSS 11.0 and SAS 9.0 software, after advice from Mrs. Helen Brown, Information and Statistics Division, National Health Service for Scotland. The risk assessment score proposed in Chapter 7 was designed together with Mrs. Helen Brown.

The thesis has been prepared by myself, using a Dell Inspiron 5000 computer, an Epson Stylus 760 Ink jet printer, an Epson Perfection 1200 scanner and the following software: Microsoft Word 2000, Microsoft Excel and Presto! Page Manager for Epson (New Soft Technology Corporation) and Reference Manager 9.5 (ISI Research Soft).

This thesis has not been previously submitted, in part or in whole, for consideration for any other degree, postgraduate diploma or professional qualification.

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First of all, I would like to thank Mr. John Forsythe for his generous support and guidance throughout my research appointment. His confidence in the success of the project (even when I though it was leading to nowhere) and determination to complete the work within two years were very stimulating. I hope that at the end of my research appointment I have achieved more than just writing this thesis, and managed to acquire some of his eloquence and diplomatic skills.

Secondly, I would like to thank everyone in the transplant unit at the Royal Infirmary for their cooperation and advice and for the family environment provided during these two years.

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Finally, I would like to apologize to my daughter Maria for being away most of the time during these two years and for missing many of the milestones of her early childhood. I hope this thesis is a small but worthy compensation for the time I denied her. Most of all, I would like to thank my wife Anca for her constant encouragement and for being the pillar of our family during the conception and completion of this thesis.

Last, but not least, I would like to thank my parents, without whom, none of these would have been possible. This thesis is a testimony of their dedication and efforts in my upbringing.

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ABSTRACT

As in the rest of the world, renal transplantation in Scotland is under tremendous pressure due to increasing demand but a limited supply of donor organs. In this setting issues of organ allocation, equity of access, standards of the assessment process and appropriateness of transplantation in certain groups of patients become very important indeed. This thesis set out to answer the following questions:

1. Are there any benefits of regional kidney sharing alliance?
2. Is there equity of access to the transplantation service? If not, which are the sociodemographic and comorbidity factors which may be responsible for these differences?
3. Does transplantation provide a survival advantage over dialysis in various renal failure populations? Is there any benefit in transplanting high-risk groups of patients?
4. Can the risk factors identified at the assessment process be quantified into a patient survival risk score?

An initial analysis examined the current organ allocation system and the activity of the new Scotland-Northern Ireland kidney sharing alliance. This study showed a substantial benefit of a wider regional sharing alliance, with an improvement in the proportion of favourable matched kidneys and a higher organ exchange rate without any detrimental effect on the length of the cold ischaemic time or graft survival.

A study of equity of access to transplantation showed that women, elderly patients, diabetics, patients starting replacement therapy on haemodialysis and patients starting dialysis in a renal unit which is not adjacent to a transplant centre are less likely to be listed. Age, the primary renal disease and centre of listing are predictors of access to transplantation, once listed. In addition, left ventricular hypertrophy, respiratory or cerebro-vascular diseases exert a negative effect on the speed of access to the renal transplant waiting list, while access to transplantation is diminished for those with cardiac arrhythmias and hyperparathyroidism.

Survival on dialysis and transplantation were compared. Transplant recipients have a 68% lower long-term risk of death and a 3.6 times better life expectancy compared with patients on dialysis on the transplant waiting list. The magnitude of this survival benefit is not equal for all, but it is present even in high-risk groups of patients such as elderly recipients or patients with diabetes.

There are significant variations in the assessment of the renal transplant candidate between the four transplant centres in Scotland. Results highlighted a lack of consensus, particularly with regards to the high-risk patients.

The sociodemographic and comorbid conditions were quantified into a survival risk score. This allowed the prediction of survival on dialysis or after transplantation, based on an individual patient's general health at the moment of listing. Using such a score, patients could make an informed decision regarding the benefits and the risks associated with either form of treatment.

ABBREVIATIONS:

ALD	Alcoholic liver disease
BMI	Body mass index
BSD	Brain stem death
COAD	Chronic obstructive airways disease
CAPD	Chronic ambulatory peritoneal dialysis
CCPD	Chronic cycling peritoneal dialysis
CTS	Collaborative Transplant Study
CVD	Cerebrovascular disease
CVA	Cerebrovascular accident
CMV	Cytomegalus virus
DNA	Dezoxy-rybo-nucleic acid
ESRD	End stage renal disease
GI	Gastrointestinal
GN	Glomerulonephritis
GORD	Gastro-oesophageal reflux disease
HD	Haemodialysis
HLA	Human leukocyte antigens
HSP	Highly sensitised patient
IHD	Ischaemic heart disease
IN	Interstitial nephritis
IQR	Inter-quartile range
LVH	Left ventricular hypertrophy
MHC	Major histocompatibility system
MS	Multisystem disease
PCR	Polymerase chain reaction
PE	Pulmonary embolism
Pmp	Per million population
PRA	Panel reactive antibodies
PVD	Peripheral vascular disease
PTH	Parathormone
RR	Relative rate
RRT	Renal replacement therapy
SEM	Standard error of the mean
SRR	Scottish Renal Registry
TIA	Transient ischaemic attack
TURP	Trans-urethral resection of prostate
Tx	Transplant
UKT	United Kingdom Transplant
UNOS	United Network for Organ Sharing
UNOS	United Network for Organ Sharing
USRDS	United States Renal Data System
WL	Waiting list

CHAPTER 1

INTRODUCTION

1.1 SHORT HISTORY

Transplantation is one of the youngest and fastest developing fields of medicine. It was only in 1954, when after decades of unsuccessful experiments around the world (1-3), that Murray and Merrill performed in Boston the first successful kidney transplant between identical twins. They wrote the first page in what was going to be a fascinating success story in medicine. In less than half a century, more than half a million people received a second chance for life by means of a solid organ transplant. Liver, heart, lung, heart-lung and pancreas transplants were introduced (4-8) and are now established therapeutic options.

Other procedures such as live partial liver transplants (9;10), intestinal transplantation (11), islet-cell transplantation (7), although still in their infancy are rapidly gaining their place as accepted treatment modalities. `During the last decade, xenografts from genetically engineered animals (12), stem cell technology and the mapping of the human genome have opened a new dimension for transplantation.

Better technologies for organ storage and transportation (13), antigen screening and typing have been developed (14). Although we have not yet found the Holy Grail of immune tolerance, we are a few steps closer to complete control of rejection due to an incredible array of immunosuppressive medication.

The field has seen numerous advances in public policy and legislation. Brain stem death was accepted in the UK in 1976 (15) and laws and codes of practice aimed at regulating transplantation activity have been enacted (16). National networks and international alliances for obtaining and allocating organs have come into being,

together with improved allocation schemes and recipient selection guidelines (17;18).

1.2 BENEFITS OF RENAL TRANSPLANTATION

Renal transplantation has evolved tremendously since the days of Murray and Merrill from being an occasional procedure into the "gold standard" treatment for patients with end stage renal failure.

It is widely accepted nowadays that transplantation provides the best chance of survival with a reduced risk of death and a projected life span twice longer when transplant recipients are compared with those who remain on dialysis (19). However, comparative survival rates for various treatment modalities are difficult to construct, as often data in the literature do not reflect the fact that patients change treatment modalities frequently and that the characteristics of those selected for each modality may differ significantly. Several risk factors and associated medical conditions can adversely affect survival and therefore should be taken into account in any comparison between therapeutic modalities. It has been suggested that patient's state of health rather than the treatment modality itself is the most important factor determining survival (20). Even with these caveats in mind, one cannot dismiss the increasing amount of evidence from carefully constructed analyses showing a reduction in the relative risk of death if a patient receives a transplant rather than continues on dialysis. (19;21-23).

Most studies have shown that the quality of life of patients receiving a transplant exceeds that of patients receiving dialysis (24;25). The obvious benefit of transplantation is freedom from the constraints of dialysis. On average, patients spend 40 to 50 hours a month receiving haemodialysis (HD), 60 to 70 hours receiving chronic ambulatory peritoneal dialysis (CAPD) or 280 hours receiving chronic cycling peritoneal dialysis (CCPD). A successful transplant will save a patient nearly 100 days a year which results in a greater flexibility and independence, an increased earning potential and increased family and personal time (26). Life satisfaction, physical and emotional well-being and the ability to return to work or school are all significantly better in transplant recipients than in dialysis patients.

A successful kidney transplant is more cost-effective to the health care system than haemodialysis. Although most of the data on the economic aspects of transplantation comes from the United States, where a transplant provides a relative net saving after a period of 3-4 years (27), this cost effectiveness was seen in all countries that have developed a renal transplant programme (28). In the United Kingdom, transplantation costs on average £15000 to £25000 in the first year, with an estimated cumulative cost of around £1500 to £3000 for each subsequent year, due to reduction in immunosuppressive medication (29). Compared to an estimated annual expense of £12000-18000 for peritoneal dialysis and £20000-25000 for haemodialysis, renal transplantation provides significant economic advantages, which are achieved today when the one-year graft survival is exceeding 85%.

1.3 RENAL TRANSPLANTATION RESULTS

The "Transplant activity report 2000" published by UK Transplant (30) showed a one year and a 5-year transplant survival estimate after first cadaveric kidney transplant of 86% and 69% respectively (table 1.1)

Transplant survival time	Year of transplant	No. analysed	Survival estimate (%)	95% CI	% follow-up
One year	1997-1998	2222	86	85-88	80
Three years	1995-1996	2681	77	76-79	87
Five years	1993-1994	2722	69	67-71	79

Table 1.1 Transplant survival after first kidney only transplant in UK and Republic of Ireland, 1993-1998. (*Source: UK Transplant Activity Report 2000)*

Looking at changes in survival over time (table 1.2), one can see that there has been a constant increase in one-year transplant survival rates as well as an improvement in the estimated kidney half-life. (Log rank test, p=0.006).

	Kidney half-life		One year transplant survival	
Year of graft	Estimate	95% CI	Estimate	95% CI
1984 - 1986	9.8	9.0 – 10.5	74	72 – 76
1987 – 1989	9.3	8.7 – 9.9	80	78 – 82
1990 – 1992	11.6	10.7 – 12.5	82	80 – 84
1983 - 1995	14.0	12.5 – 15.6	83	82 – 85
1996 - 1997	13.5	12.5 – 15.6	85	83 - 86

Table 1.2 Kidney half-life and one year transplant survival estimates for first adult cadaveric kidney by year of transplant, January 1984 – December 1997

(*Source: UK Transplant Activity report 2000)*

Similar improvements were seen in the one-year survival rates for living donor kidney transplants (*appendix, table A.1, page 330*). In addition, an analysis of patient and graft survival at one, three and five years following cadaveric kidney transplants revealed that 96% and 87% of the patients survive at one and five year respectively, while 88% and respectively 76% of the grafts are functional at the same time points *(appendix, table A.2, page 330)*.

Recent data from the United States Renal Data System (USRDS) (31) showed an improvement from 74.7% to 88.8% in one-year graft survival following first cadaveric kidney transplants and from 86.1% to 94.5% in one-year graft survival for first living donor transplants over a ten-year period (figure 1.1). These short terms results were associated with a 17% improvement in the five-year survival following

first cadaveric kidney transplants *(appendix, table A.3 page 331)*. Even so, the most recent data from USA show that the 5-year graft survival is 18% lower than in UK for the same period (58% in USA vs. 76% in UK, 1990-1992) *(appendix, tables A.2, page 330 and A.3, page 331)*.

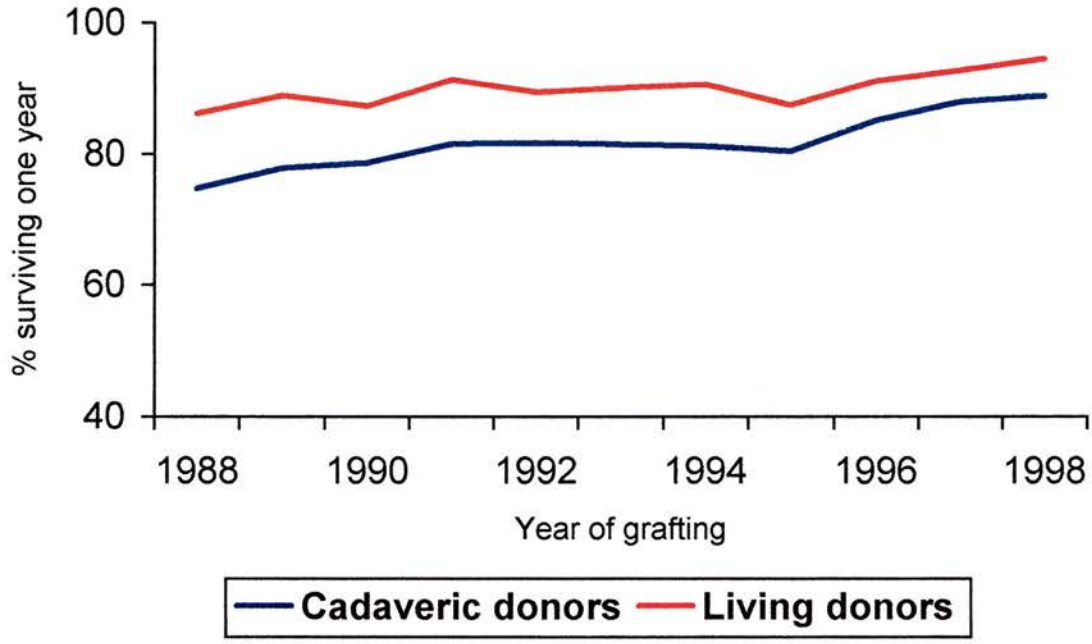


Figure 1.1 One-year graft survival rates following first cadaveric and living donor transplants in USA 1988-1998 (*Adapted from "The 2001 USRDS Annual Data Report Atlas")*

Data from 15 European centres collected by the Collaborative Transplant Registry Study showed that the 5 years survival for a first kidney transplant exceeds 68% for graft (figure 1.2) and 85% for patient survival.

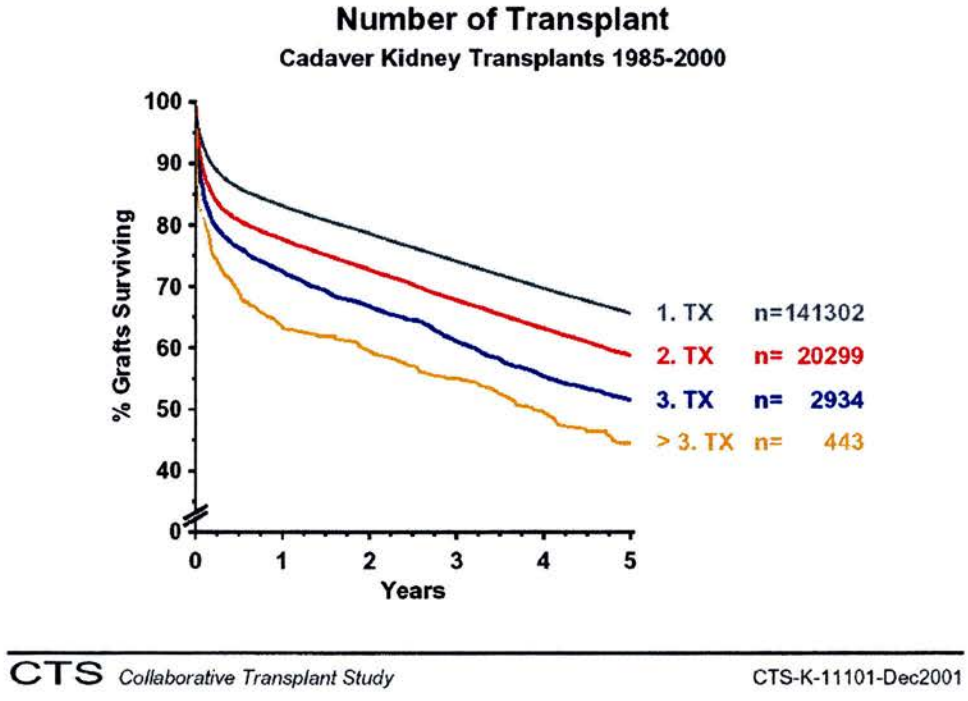


Figure 1.2 Graft survival for cadaveric kidney transplants in Europe 1985-2000 (1st graft vs. regrafts). (*Source: Collaborative Transplant Study)*

1.4 DEMAND AND SUPPLY OF TRANSPLANTATION

On 31st of January 1968, Sir Peter Medawar opened the Nuffield Transplantation Unit at the Western General Hospital in Edinburgh. In his address he said: "... We cannot hope that medicine and public health and humane social legislation will preserve all of us into advanced old age, and at the same time reasonably expect that the supply of human tissues and organs for transplantation will measure up to what is likely to be the demand." Those were prophetic words as today the demand for transplantation exceeds by far the supply available. The benefits of renal transplantation have lead to increasing numbers of end stage renal disease (ESRD) patients being referred for transplantation.

A recent report from the Scottish Renal Registry (SRR) (32) has shown that the incidence of ESRD in Scotland is rising (figure 1.3) and is now exceeding 108 new patients per million population (pmp).

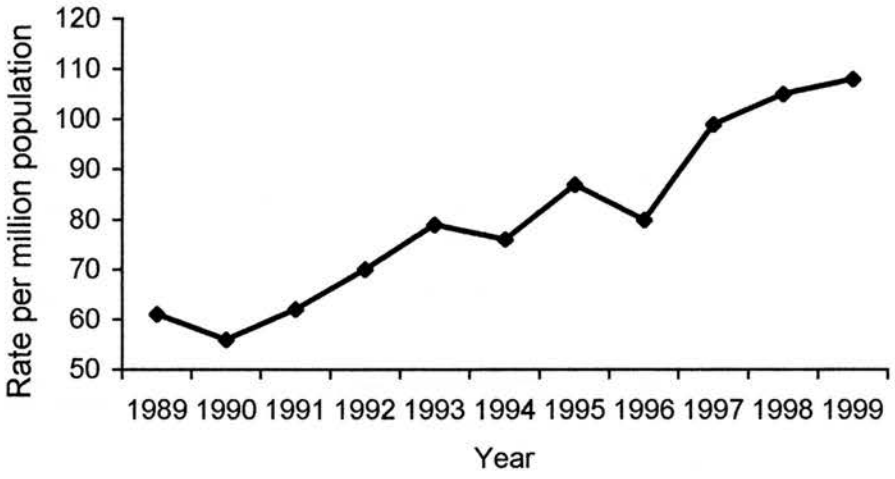


Figure 1.3 Annual incidence (pmp) of new patients with ESRD in Scotland 1989 – 1999. (*Source: Scottish Renal Registry)*

According to a UK Renal Survey (33), the UK national incident rate in 1998 was slightly lower, at 94.6 pmp. There is a significant variation between the acceptance rate in England, Wales, Scotland and Northern Ireland ($p<0.0001$, Poisson regression), with the lowest rate in England (table 1.3). Given the larger ethnic minority in England, the low rate suggests that there may be an underestimated need for RRT in this part of the country.

	Scotland	England	Wales	N. Ireland	Total UK
Acceptance rate pmp	105	92	128	107	96
(95% CI)	(96–114)	(90–95)	(115–141)	(92–124)	(93–98)

Table 1.3 Variations in acceptance rate for RRT in UK in 1998 (*Source: The Renal Registry 2000 Report)*

The more recent UK rates are unknown as no further surveys were carried out and the Renal Registry data accounts for only 40% of the units in England and Wales compared with 100% in Scotland. Nevertheless, based on available data, it is expected that the rate is rising across the whole of the UK.

A report by the European Renal Association (ERA-EDTA) has shown that the need for replacement therapy is increasing in most European countries, the highest incidence of new ESRD patients being noted in Belgium (165 pmp) while the lowest is in Norway (89 pmp) *(appendix, figure A.1, page 331)*.

Worldwide, the problem of ESRD is growing at an alarming rate. In 2000, in USA alone, over 300.000 people were on maintenance dialysis. The number increased at an annual rate of 6% between 1992 and 1996 and by 4% between 1997 and 2000 *(appendix, table A.4, page 331)*. The ESRD annual incidence rate in USA was 317 per million population in 1999, by far the highest in the world (figure 1.4). With accurate identification and reporting of ESRD cases in more countries, it is certain that these figures will change significantly in the near future.

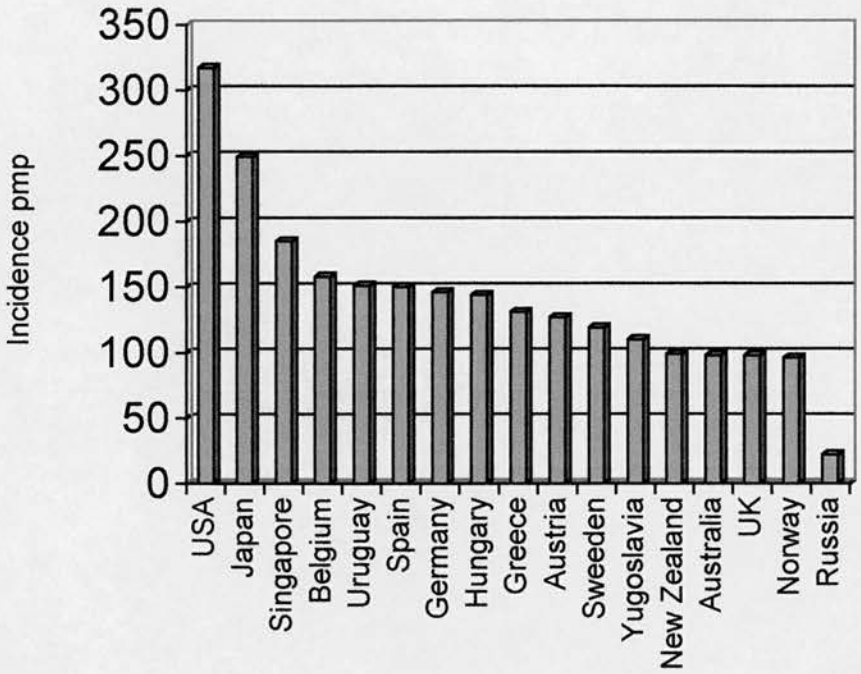


Figure 1.4 Annual incidence of new ESRD patients (pmp) in 1999 (*Source: The 2001 USRDS Annual Data Report (31))*

As many of these patients have been or will be referred for transplantation, clearly, the supply of donor organs could not keep pace with such an increasing demand. The effects were quick to follow: a constant increase in the length of time spent waiting on the list (figure 1.5) and a higher number of patients dying while waiting for a transplant (table 1.4).

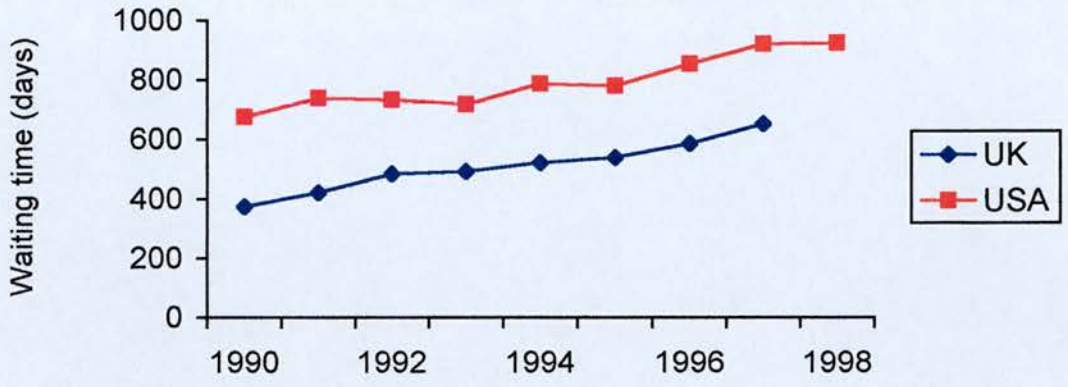


Figure 1.5 Changes in the median waiting time on the active list for a kidney transplant in UK and USA, 1990-1998. (*Source: UK Transplant and USRDS)*

Year														*Total*
1988	*1989*	*1990*	*1991*	*1992*	*1993*	*1994*	*1995*	*1996*	*1997*	*1998*	*1999*	*2000*	*2001**	
800	784	951	995	1080	1320	1390	1538	1854	2053	2419	3205	2841	1307	22537

Table 1.4 Reported deaths on the waiting list for a kidney transplant in USA, 1988-2001 (*Source: UNOS, * - until October 2001)*

Moreover, in many countries, including the UK, the cadaveric donor pool has been shrinking. The number of patients waiting for a kidney transplant in United Kingdom has increased by about 45% in the last decade on a background of a 10% reduction in the number of cadaveric donor organs (figure 1.6). Other European countries, despite significant variations in donation rates, have seen a similar increasing gap between demand and supply.

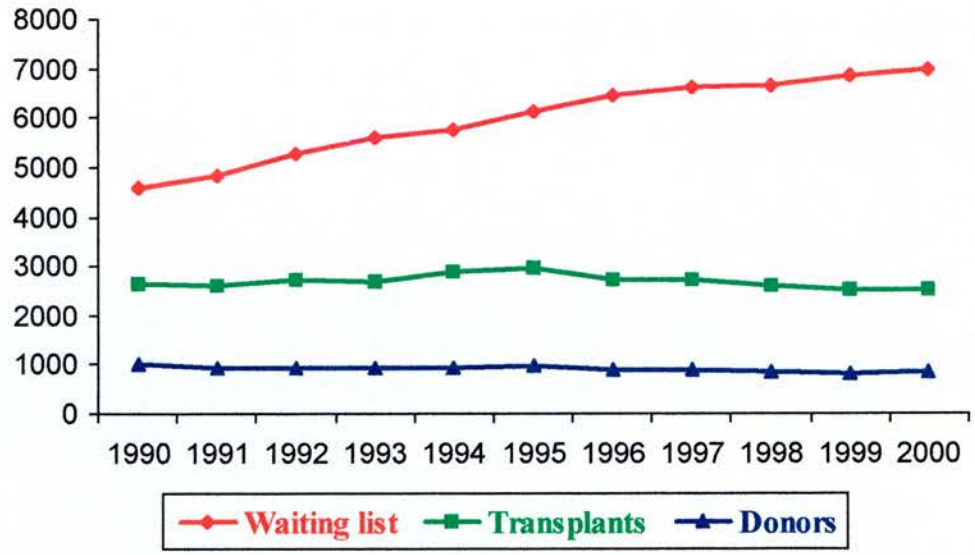


Figure 1.6 Number of cadaveric donors and transplants in the UK and Republic of Ireland and patients on the waiting list at 31 December, 1990-2000 (*Source: UK Transplant Activity report 2000 (30)*)

In the USA, the slow but steady increase in the number of donated kidneys in the last decade (table 1.4) was not enough to resolve the demand of over 50.000 patients waiting for a kidney transplant in September 2001.

Year Donor Recovered											
1990	*1991*	*1992*	*1993*	*1994*	*1995*	*1996*	*1997*	*1998*	*1999*	*2000*	*2001**
4304	4268	4276	4609	4795	5000	5038	5082	5343	5373	5488	1283

Table 1.4 Number of cadaveric kidneys recovered in USA, 1990-2001 (*UNOS, Annual Report 2001)(*- until October 2001)*

Many reasons are responsible for the reduction in donation rates, including a decrease in the rate of fatal road accidents, an ageing process of the donor population (figure 1.7), procurement arrangements and lack of a coordinator network, insufficient funding and lack of intensive care unit beds, cultural and religious attitudes, family refusals as well as health professionals training and legislation. Each of these factors will have to be addressed if we are to improve the current situation.

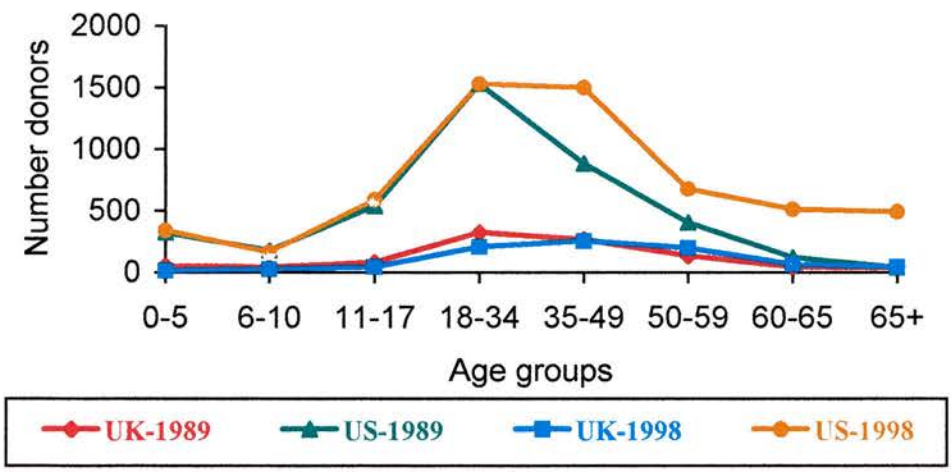


Figure 1.7 Changes in the age distribution amongst the cadaveric organ donors in UK and USA (*Source: UK Transplant and UNOS)*

And there is evidence that improvements are in our grasp, various studies estimating the true potential for donation in the region of 45-50 donors per million population (34). Moreover, the Spanish system has shown the way, successfully increasing donation rates for over a decade and achieving the highest rates worldwide (figure 1.8).

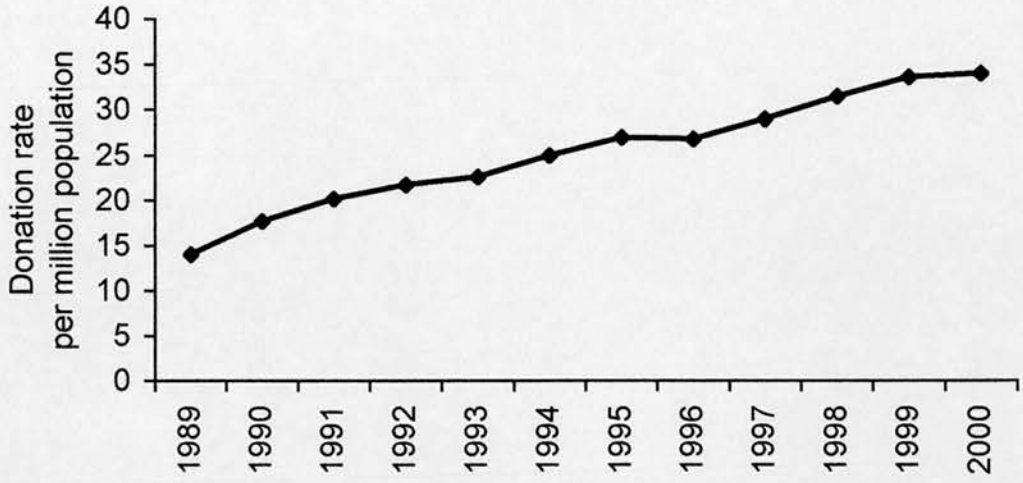


Figure 1.8 Donation rates per million population in Spain 1989-2000 (*Source: ONT – Organisation Nacional de Transplantes)*

The Spanish miracle, as it often has been called, is in essence a huge organisational success, with an extensive coordinator network in every hospital, (35) excellent cooperation between autonomous regional organisations and a national coordination agency whose role is merely promoting the transplant and donation activity (36). Several countries have been adapting this model to local conditions and hope to see significant improvements in donation activity (37;38).

Most of the changes in the organisation of donation cannot be separated from the legislation governing this activity (39). The donor's legal situation varies across the globe (table 1.5)(40). In some countries, an "opt-in" law, which requires "informed consent" from the relatives prior to proceeding to donation, is in place. Most

European countries have adopted the so-called "opt-out" or "presumed consent" law, whereby organs are removed from every identified donor unless they have expressed their wishes against donation ("Hard form" opt out) or after inquiring from the relatives whether they were aware of such wishes ("soft form" opt out). The only notable exceptions are UK where coordinators have to register the "lack of objection" from the relatives and USA where physicians have to prove that donation was requested from the relatives (technically, both are forms of informed consent).

Country	Donation rates (pmp)	Donor's legal situation
UK	**13.4**	**Lack of objection**
USA	**22.3**	**Required request**
Italy	15.3	Informed consent
New Zealand	10.7	Informed consent
Australia	10.2	Informed consent
Eurotransplant	14.4	
Austria	24.3	Presumed consent
Belgium	25.6	Presumed consent
Netherlands	12.6	Informed consent
Germany	12.2	Informed consent
Scandiatransplant	14.3	Presumed consent (except Denmark)
Spain	**33.9**	**Presumed consent (soft)**
Portugal	19.5	Presumed consent
France	17.0	Presumed consent (soft)

Table 1.5 Donor's legal situation and donation rates in various countries in 2000.

There is an endless debate whether an "opt-out" law is better than "opt-in" and whether it would be ethically and morally acceptable as a basis for the donation

activity. Beyond the philosophical disputes, there is substantial evidence that the introduction of a decentralized organ procurement system has lead to a significant increase in the number of organ donors (41;42). It is yet unclear whether replacing an "informed consent" with "presumed consent" legislation has a similar effect on organ donation rates, but some studies (43;44) suggest that a significant increase was noted in countries where the change in legislation was adopted.

In an attempt to increase the number of transplants, live donation has been revisited. There is an increasing drive in the transplant community to promote this type of transplantation, as it leads to a better long term outcome compared with cadaveric renal transplants irrespective of whether the donor is related or unrelated to the recipient (45). Furthermore, the availability of a live kidney donor allows a more accurate timing of transplantation, making pre-emptive transplantation (before the onset of dialysis) possible or reducing the length of time on dialysis, both with a beneficial effect on long-term graft function (46-48). Although the living donor rate in UK has increased by a factor of four in the last decade, at 5.3 per million population in 2000 it is still much lower than some other countries (Norway: 17 per million population, Sweden: 10.1 pmp) (49), but regional experiences have shown that there is a great potential for this form of transplantation (30).

The widening of the acceptance criteria for donors (50-52) together with asystolic donation (53-57) are just a few of many other ways in which we seek to correct the deficit of donor organs. But for a complex problem there is no simple answer. Until we find an endless supply of donor organs (such as genetically engineered xenografts

(12;58;59)) or eradicate renal failure, we have to accept that not all patients will have access to a renal transplant and there is a need for an objective and fair way to allocate kidneys, which should also provide the best outcome.

1.5 ORGAN ALLOCATION

1.5.i Ethical dilemmas

As the supply diminishes, the transplant community has come to accept that the question is not why but how to ration the resource. How then should donated organs be allocated? The typical answer is "fairly" or "equitably", but the problem is to determine the meaning of those terms in the special context of organ transplantation. The allocation of cadaveric kidneys for transplantation confronts the decision makers with a web of competing responsibilities: to maximize graft survival, to improve patient quality of life and life expectancy, to minimize waiting times and to promote equity across a range of socio-demographic dimensions (60). No single set of criteria is likely to meet all these demands in the complex medical, ethical and social reality of organ allocation.

Furthermore, transplantation is a complex process, with several layers of decision making and multiple deciders (60-63). Organ allocation only tackles the last two steps of the process (figure 1.9), as patients with end stage renal disease must be first of all identified, referred for evaluation and accepted as potential recipients. Any attempt to address the ethical and practical issues surrounding organ allocation must therefore not lose sight of the wider context of the selection process and the values and principles that prevail at each stage.

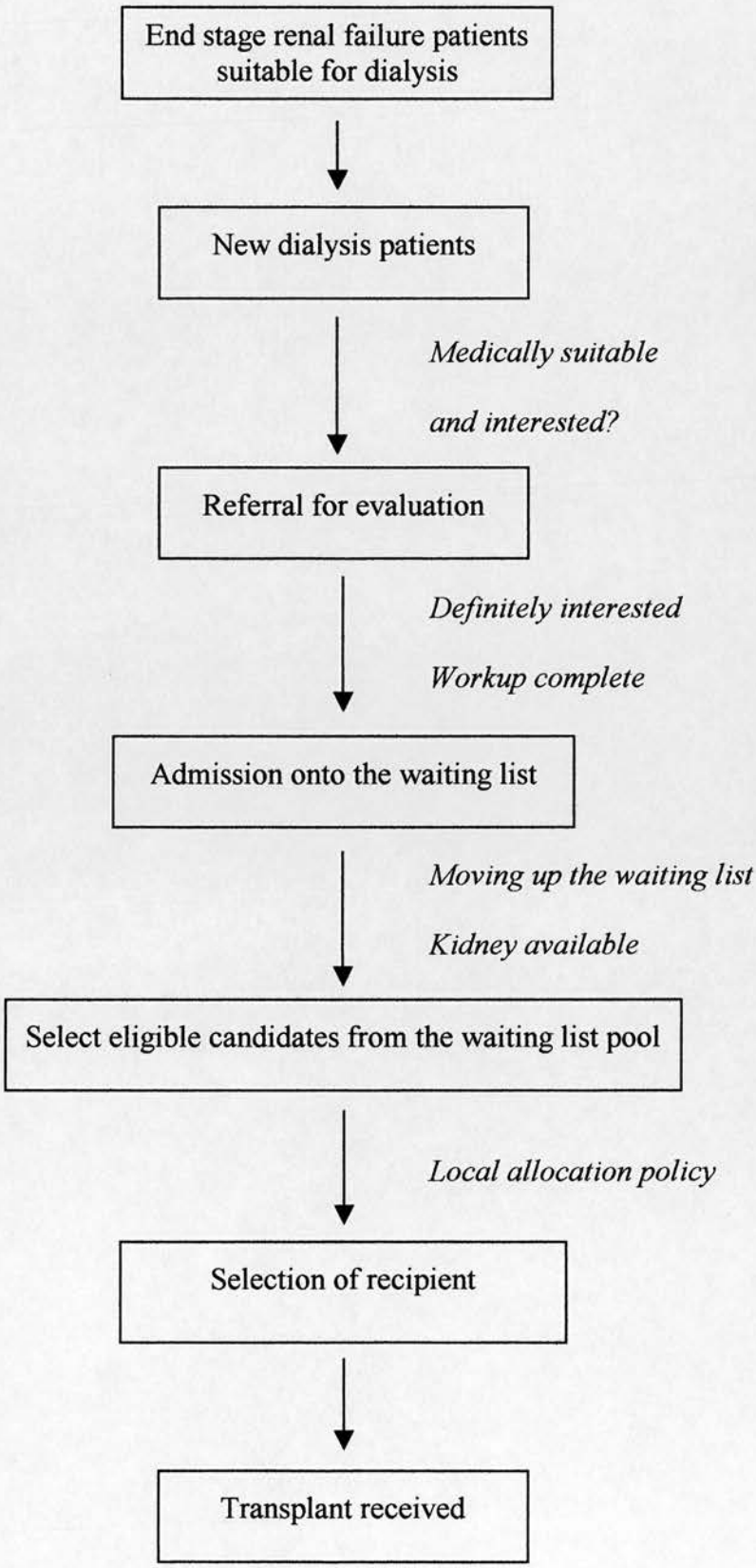


Figure 1.9 The cadaveric renal transplantation process

In facing rationing decisions, there are many philosophies that can be adopted (64-68), but whichever we choose, it has to incorporate the basic principles of medical ethics:

i.) Beneficence (doing good for the patient)

ii.) Primum non nocere (avoid harming the patient)

iii.) Respect for patient's autonomy

iv.) Justice (promote fairness).

Two of the most important concepts in medicine are *justice* (equity in distribution) and *utility* (providing the 'best' outcome for the 'majority' of the patients) (69;70). Applying purely a justice concept, the transplant process should provide equal access to those in need. Several interpretations of this principle have been proposed, from radical solutions (*e.g.* if the resource is too scarce so not everyone has access to it, then nobody should (71)), through random lottery (72) and a more neutral queuing (*e.g.* first-in-first-out (67)), to prioritisation of specific groups of patients (*e.g.* most critically ill, rare blood groups, or those waiting longest (73)).

On the other hand, if the principle of medical utility would be given primacy, transplantation would provide only for patients who are likely to have the best outcome (*e.g.* young versus elderly patients, first transplant versus re-transplants), who are the most deserving (*e.g.* the mother-of-two versus the drug addicted alcoholic), who make the greatest contribution to society (*e.g.* the scientist versus the lorry-driver)(67). Such a strict principle would discriminate on the grounds of age, race, gender, social status, religious or political beliefs and is generally unacceptable.

It is important to acknowledge that fairness may not always be compatible with achieving the greatest overall good, as exemplified above. Both principles must be applied in a broad sense (74;75). The problem is further compounded by the deontological tradition (69;70) of our medicine whereby the physician has a duty to his/her patient even in the face of a poorer prognosis (*e.g.* offer transplantation to a patient that has already lost three grafts to recurrent disease). Clearly, the whole process of selecting transplant candidates and allocating organs is a value-laden issue. Many of the difficult ethical questions surrounding transplantation are rooted in conflicts of values (figure 1.10), which are not between good values and bad values, but rather between one important value and another.

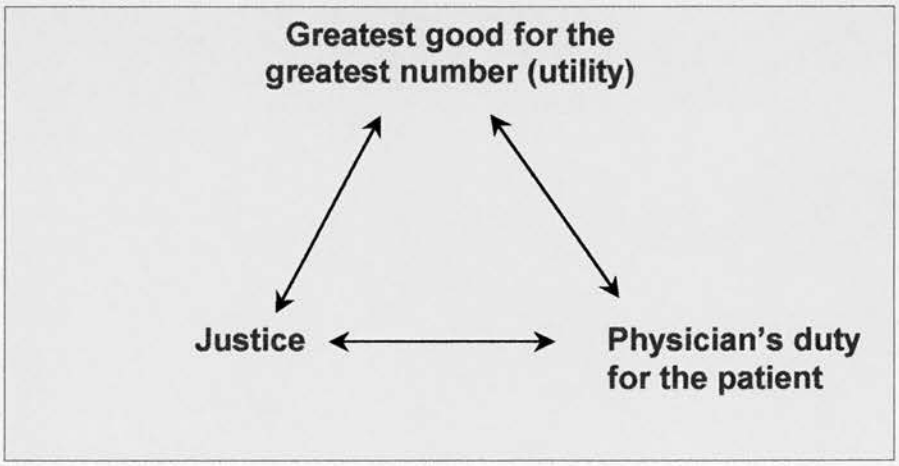


Figure 1.10 Ethical dilemmas in transplantation

A number of philosophers have cast doubt on whether all things that we rightly value can be combined into a single framework (76;77), and the same may be true in seeking agreement on patient selection and allocation criteria.

Whatever the ethical principle, deciding eligibility for the transplant waiting list and transplantation has to take into account some degree of efficacy, in other words, an implicit expectation that transplant success must be higher than some minimum standard. Yet, how low or high this minimum should be set has not been formally agreed (62), but it should certainly consider all medical and non-medical factors (social, economical, life-style, family support, emotional, cultural) which impact on outcome (63). There are two further important points on this issue: a defined minimum acceptable level must be reviewed and evaluated periodically, as overall results of transplantation change rapidly and hence the significance of the chosen level may be obsolete. Secondly, but equally important, a minimum standard should not be used as a cloaking device for biases against certain groups of patients (*e.g.* high-risk ones) (78).

The best way to address these conflicts of value is through sustained discussion among informed and thoughtful individuals representing all those involved in the transplantation process (care-takers, patients, funding organisations). Making these kind of decisions is difficult, but we owe it to the public (on whom we rely for altruistic donation) to do it in an open manner and to ensure that criteria guiding these judgements could be acknowledged as the best available by all to whom they apply. As philosopher Thomas Scanlon has suggested, an act can be justified if it follows from a system of rules that, on reflection, cannot reasonably be rejected by anyone seeking informed, unforced, general agreement about the matter in question (79).

1.5.ii Principles of allocation schemes

Beyond the ethical dilemmas surrounding transplantation and organ allocation, there is the question of practicality. On what basis should we allocate available donor kidneys? It can be argued that there are six major factors to be considered in cadaveric kidney allocation (80):

a. Immunological factors (e.g. ABO group compatibility)
b. Regulatory factors (e.g. legislation)
c. Outcome (patient rehabilitation, graft survival)
d. Access to organs
e. Costs (to the society and patient)
f. Effects on the total pool of organs

Any practical allocation system must be devised within the constraints of the first two factors and have a sizeable effect on the remaining four. Unfortunately, there is such a strong interaction among these variables that devising a method or an algorithm, which will reach a well-grounded agreement on these matters would be practically impossible. But this should not stop one from trying to develop a scheme, which is acceptable for a particular society's medical, ethical and practical settings.

Since the early days of transplantation, there have been attempts to devise a way to allocate kidneys, based on factors that have a significant impact on outcome and provide an additional efficacy for transplantation over alternative ways of treatment. The founding fathers scientifically demonstrated a genetic basis for allograft rejection (81-83) and noted a substantial benefit of HLA (human leukocyte antigen)

matching on graft survival (84). Most allocation schemes, which were developed until the present day are based on this finding and have the HLA matching as the foremost principle.

1.5.iii HLA system as the basis of kidney allocation

After several unique discoveries in organ transplantation, it has become clear that rejection and acceptance of a particular transplant organ are inherited characteristics. An array of inherited cell-surface antigens (proteins) defines the "foreign" nature, or allogeneity of transplanted organs and tissues. The genes that encode for these proteins are termed *histocompatibility genes* and are located on different chromosomes in each species. Because of its central role in antigen recognition and transplant immunobiology, this group of genes has been defined as the *major histocompatibility complex* (MHC). The human MHC complex, known as the *human leukocyte antigen* (HLA) system, is a genetic region located on the short arm of the chromosome 6 (6p21.3) which contains over 200 genes (85;86). Six HLA loci have been identified, with an extensive polymorphism, some with more than 300 alleles (87), which make the HLA system the most polymorphic system found in humans.

The HLA antigens can be grouped into two different classes based on their structure and cellular distribution. There are some 20 Class I molecules of which HLA-A, -B, -C are the most important from an immunological point of view. They are expressed on most nucleated cells and bind and present peptides derived primarily from

endogenously synthesized proteins (e.g. viral proteins) to $CD8^+$ T cells. Class II molecules are named HLA-DR, -DP, -DQ and have a more restricted distribution than Class I because they are generally expressed by *antigen-presenting cells (APCs)* such as monocytes, macrophages, dendritic cells, renal mesangial cells, Kupfer cells, alveolar type 2 lining cells and other elements of the immune system such as lymphocytes and thymic epithelial cells (88).

The HLA molecules have a fundamental role in T-cell activation (figure 1.11), which become reactive to "foreign" tissue and mount a formidable attack that culminates in the destruction of the graft. This process is part of a complex chain of events, which is as yet not fully understood (89).

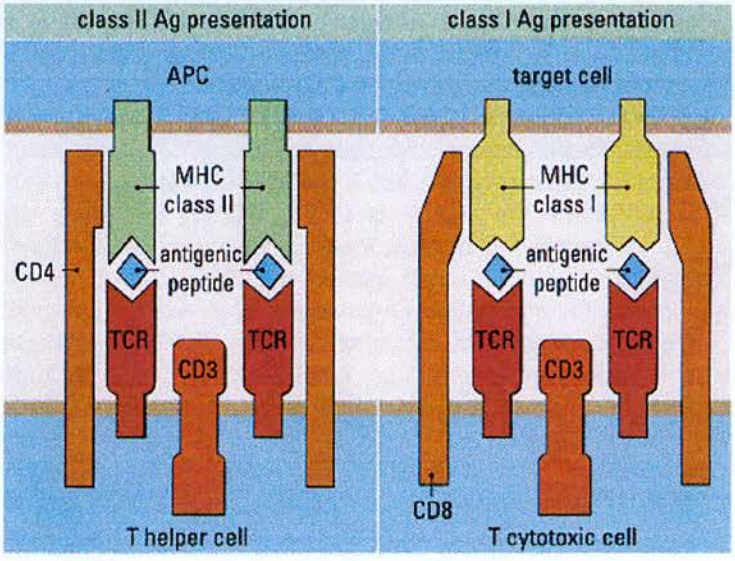


Figure 1.11 Immune recognition by T cells and the role of MHC molecules in antigen presentation (TCR = T cell receptor, APC = antigen presenting cell)

The remarkable degree of polymorphism of the HLA antigens accounts for the great difficulty in tissue matching, as opposed to the relative ease of matching for the less polymorphic ABO blood group antigens. More than 81 HLA-A, -B and -DR antigens can be detected using serologic methods *(table A.5, appendix, page 332)*, and at present, most laboratories use a microlymphocytotoxicity test (14) in which antibodies are allowed to react with the lymphocytes to be typed in the presence of rabbit complement. More recently, several DNA based HLA typing methods have been developed. DNA-based typing offers several advantages over serology:

- Typing can be performed on any tissue containing nucleated cells (*e.g.* buccal swabs)
- Samples can be stored dried without refrigeration for long periods of time
- The accuracy of DNA typing is better than that achieved using serology and the more difficult HLA specificities, those for which highly specific alloantisera are rare or not widely available can be easily determined using this method.

Once the HLA typing of a potential recipient has been determined, a second test is carried out. This estimates the probability that a patient will have a positive donor crossmatch, in other words has antibodies against the HLA molecules of the donor (*sensitised)*. This test is very important, as the detection of a high level of anti-HLA antibodies (*panel-reactive antibody –PRA)* leads to a lower probability of finding a crossmatch–negative kidney. In a simplistic way, the finding of 75% PRA in a test

suggests that 75% of donors will be unacceptable for the patient because they have circulating antibodies that react with one or more of the donor's HLA antigens and therefore they are exposed to a higher risk of graft rejection.

The importance of HLA matching in determining the graft outcome is now well established (90-93). Large analyses from the UNOS and CTS databases showed that graft survival decreases in a step-wise manner with poorer HLA matching (figure 1.12).

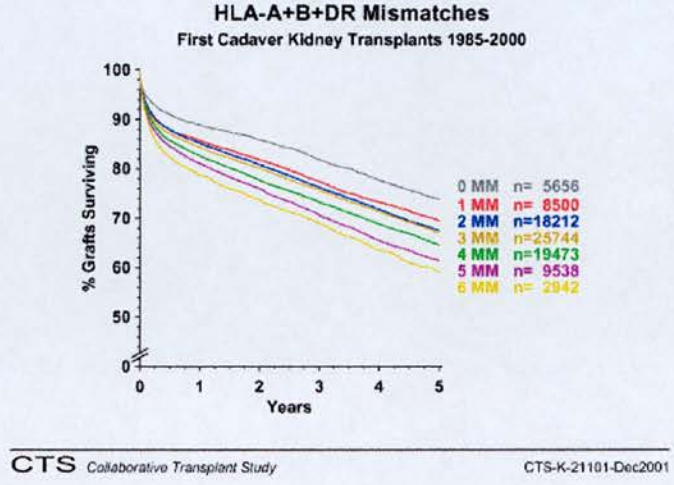


Figure 1.12 Relationship between graft survival and HLA matching

The effect of HLA matching on graft outcome is persistent even under the condition of short ischaemia (0-6 hours) and is enhanced in pre-sensitised patients (PRA > 50%).

But HLA matching has not been always accepted as a determinant of outcome, except for transplants involving the complete match (*full-house match: 0 HLA-A, 0*

HLA-B, 0 HLA-DR mismatches) (94;95) and one must acknowledge that the differences between each individual step of mismatch are very small (figure 1.12). Nevertheless, results from a complex multivariate analysis of the factors affecting the graft outcome in UK (96) have shown a substantial benefit of a complete match over all other matches, while any HLA-DR mismatch will lead to the worse graft outcome. The analysis also revealed that 110 (*1 HLA-A, 1 HLA-B, 0 HLA-DR*) mismatches did not differ significantly from 100 (*1 HLA-A, 0 HLA-B, 0 HLA-DR*) and 010 (*0 HLA-A, 1 HLA-B, 0 HLA-DR*) mismatches in terms of transplant survival (table 1.6). This suggests that the effects of HLA matching are more obvious for groups of matches rather than individual levels and this seems to be supported by other studies (97).

HLA mismatches	Overall Relative risk (95%CI) of survival	p value	Relative risk (95%CI) of survival >36 months	p value
000	0.61 (0.49-0.75)	0.0001	0.72 (0.50-1.03)	0.07
100/010/110	0.83 (0.75-0.91)	0.0001	0.85 (0.71-1.02)	0.08
All other mismatches	1.00		1.00	

Table 1.6 Relative risk of renal transplant survival after transplantation according to the level of HLA matching (Adjusted for year of graft, donor's age, recipient's age, kidney exchange, waiting time, cause of donor's death and diabetes. Baseline reference groups have a relative risk of 1.0) (*Adapted from (96)).*

Another argument used by the critics of HLA matching is that even using the current convention of matching for 75 serologically defined HLA-A and –B antigens and

considering only 10 broad HLA-DR specificities, fewer than 20% of cadaver kidneys are transplanted to an HLA-matched recipient. Furthermore, if all known alleles of HLA *(appendix, table A.5, page 332)* were used for identifying a matching kidney donor, it would be necessary to match 119 A locus alleles, 238 B locus alleles and 204 DR locus alleles in order to provide a perfect match. However impossible this may seem, there is emerging data, which suggests that matching at the allele level may result in an improvement in transplant survival (98).

This emphasis on high resolution of the HLA alleles enhances HLA differences that have evolved anthropologically. This phenomenon called *linkage disequilibrium* explains the presence of certain haplotypes within racial groups. Because grafts are preferentially assigned to patients with relatively frequent HLA specificities, HLA matching has also been criticized for diverting organs from hard-to-match recipients (*e.g.* rare haplotypes, certain racial groups) (99). It has, therefore been suggested that grouping broad HLA specificities into even broader cross-reactive groups (CREG) (99;100) tends to group individuals regardless of their racial background. The CREG are based on the fact that when an individual makes antibody, it usually reacts with a group of HLA antigens rather than individual ones *(table A.6, appendix, page 333)*. Another definition of CREGs takes into account the *epitopes* (antibody binding sites on HLA antigens) shared by cross-reactive antigens, and the whole rationale of using this approach would be that kidneys with epitopes more similar to those in the recipient are less likely to elicit a vigorous immune response.

Recent retrospective analyses revealed mixed results. Some studies suggested a graft survival comparable or better than allocation based on HLA specificities (101;102), while others suggested a worse outcome (103). Whatever the outcome of ongoing

studies, CREG does not deny the impact of HLA matching on graft survival, as a broader level of matching will be achieved anyway, but merely ensures a more equitable distribution of kidneys among various recipient groups.

Perhaps the strongest opposition to the HLA matching arises from the fact that in order to achieve a better match, a larger pool of recipients is required, which implies sharing kidneys on a wider geographical area. This could lead to longer cold ischaemic times and hence may diminish the potential benefit of better matching, but whether this is true or not remains to be determined. In addition, sharing means that centres situated in areas of high donation have to export organs to low donation centres. This could be viewed as a drain of a precious local resource, which could ultimately be a disincentive for donation.

The final argument against the use of HLA for kidney allocation was delivered by the proponents of matching when a better survival from living un-related transplants was noted when compared with better HLA-matched cadaveric kidneys (45).

Despite the pros- and cons- of how significant HLA matching is, and beyond the back stage political debates (45;104) a few statements are undoubtedly true:

1. HLA matching does influence the outcome of a kidney transplant
2. Levels of HLA matching (*e.g. 000 vs. 100/010/110 vs. all other matches)* rather than individual matches should be used in allocating kidneys
3. HLA is not the only factor that dictates the outcome and any allocation algorithm should not be based on HLA matching alone.

1.5.iv Allocation schemes and organ sharing

Most allocation systems can be defined as a two step-process. In the first step, the pool of patients with end stage renal disease is separated into two groups of eligible and ineligible candidates for transplantation with an available donor kidney. In the second step, allocation policies in place in individual systems will select a successful recipient (figure 1.9). In deciding whether a candidate is suitable for transplantation with a particular donor kidney the knowledge of the factors which influence the outcome plays an important role. Although HLA matching remains the main criterion, other donor (age, comorbidity, cold ischaemic time) and recipient factors (age, comorbidity, length of time on the waiting list, level of sensitisation, previous transplants, distance from the transplant centre) should be taken into account.

Allocation algorithms have been proposed since the early days of transplantation but following the development of powerful IT systems, computer-based point-scoring allocation schemes were implemented. It is now widely accepted that a points system leads to a structured and systematic decision (62), focusing the attention on the full range of data as well as helping to achieve an equitable selection of recipients and ensuring the public and the patients that a sound, routine plan is in place (105). Furthermore, computerised systems allow a prospective simulation and evaluation of any given allocation algorithm, eliminating the inherent bias and difficulty created by a retrospective assessment after several years of operation (106). However, the debate is still wide open with regards to which criteria should be used and especially the weight which should be given to particular factors.

The rapid development of renal transplantation and the proposal of allocation schemes brought about the concept of organ sharing. It was soon realised that in order to have a better match between the donor and recipient, wider pools of recipients/donors were required. Thus, in 1967 Eurotransplant was founded, unifying the activity of Germany, The Netherlands, Belgium and Austria. Shortly after this the United Network for Organ Sharing (UNOS) was developed in the United States through collaboration between the 15 regional organ procurement organisations (107). Other national organisations were soon developed in all countries with transplant programmes in order to optimise the use of available donor kidneys.

a. Allocation of organs for transplantation in the US

In 1987 UNOS devised an allocation scheme largely based on a local system developed by Starzl in Pittsburgh (108;109), which took into account the time of waiting, the quality of antigen matching, the pre sensitisation state and the medical urgency. There was mandatory national sharing of kidneys for recipients matched at all six histocompatibility antigens. Since then, the system has been changed twice to include kidneys with the same HLA antigens as the recipient even though fewer than six antigens were identified (1990) and in March 1995 to include zero-A, B, DR-mismatched kidneys from donors presumed to be homozygous – at least one Ag identified at each donor locus - to zero-mismatched heterozygous recipients.

The current US allocation system stipulates that there is mandatory sharing of zero antigen mismatch kidneys. ABO O kidneys should be transplanted only in O blood

group recipients except in the case of zero antigen mismatch patients who have a different blood group. The final decision to accept a particular organ rests with the transplant surgeon/physician. Due to geographic conditions in the US, there is a time limit of eight hours (defined as cross clamping of the donor aorta) for the offer to be made to the appropriate recipient centre via the UNOS Organ Centre. Once a donor has been registered, the potential recipients who have an ABO blood group compatible with that of the donor, are assigned points (table 1.7) and prioritised according to the following criteria:

1. ***Waiting time*** - The point calculation is conducted separately at three geographic levels of allocation: local, regional and national.
2. ***Quality of antigen mismatch*** - Donors with only one antigen identified at an HLA locus are presumed homozygous.
3. ***Panel reactive antibodies*** - points are allocated for PRA>80%, based upon historical or current serum sample.
4. ***Medical urgency*** is used to allocate points only at a local level.
5. ***Paediatric recipients*** - these points are retained until the candidate reaches 18 years of age. A time goal has been set to transplant paediatric recipients (*e.g.* maximum 18 months for those aged 11-17). If this time goal is not achieved, those patients receive extra points and have the second priority, after the highly sensitised patients (PRA>80%), for the non-shared kidneys.
6. ***Donation status*** - points are allocated if the recipient has previously donated within the US.

Factor	Points	
HLA mismatches	mandatory share	0- A, B, DR mm
	7 points	0- B or DR mm
	5 points	1- B or DR mm
	2 points	2- B or DR mm
Sensitisation	4 points	>80% PRA and negative crossmatch
Waiting time	1 point	longest waiting in a blood group category
	fraction of a point	all others (depending on position on the waiting list)
	1 point/year	each additional full year of waiting
Medical urgency	Points allocated only locally	
Paediatric recipients	4 points	< 11 years old
	3 points	11< age<17
Donation status	4 points	Previous donation within US

Table 1.7 Current UNOS point system for cadaveric kidney allocation

For multiple zero mismatches for the same donor, tie points are allocated in a descending sequence for identical blood groups first, and next to compatible blood type. Within both groups, priority is given to local patients, followed by paybacks (when more than 2 kidneys paybacks are accumulated) and then regional and national lists, according to the degree of sensitisation.

Alternative local allocation systems, which weigh differently the national allocation criteria, must be approved by the UNOS prior to implementation. These local variances must demonstrate that they have a sizeable impact on patient waiting time, graft survival and organ availability after three years in order to be validated. Combined transplants (kidneys and other organs) obey the same zero antigen

mismatch policy with only one kidney being shared together with the accompanying transplantable organ.

The local and national impact of this new scheme has been extensively investigated (110-116). In 1998, Hata et al. (113) published a comparative analysis of the three major changes in the UNOS allocation system and their national impact. Despite a limited follow-up period, the 1-year survival for zero-mismatched kidneys (latest change) was similar to the other HLA-matched groups: 90% for six Ag mm, 87.3% for phenotype match and 87.8% for zero mismatches. Significant changes were noted in the percentage of matched kidneys that were transplanted. 17% of the HLA-matched organs were transplanted to 6 Ag mm patients and 24% to phenotypically matched ones. There was a significant increase in the access to HLA-matched kidneys for minority recipients and this was mirrored by a similar change in the racial distribution of donors of the HLA-matched organs. These results were confirmed by other investigators (who also noted an increase in the number of long-waiting recipients that have been transplanted) both at regional (111) and national level (110).

b. Allocation of organs for transplantation in Eurotransplant

Since 1988, Eurotransplant (ET) used an allocation scheme which included a mandatory exchange for 000 mismatched kidneys. The initial system was centre oriented and was criticized for the high percentage of long waiting time patients,

inequity of access for rare HLA phenotype patients and for a growing percentage of transplantation programs with large exchange imbalances.

In 1993, Wujciak and Opelz (117;118) published the results of a computer simulated allocation scheme (XCOMB) which showed that an appropriately balanced combination of:

- mismatch grade
- waiting time
- mismatch probability
- local transplant rate
- import/export exchanges

could achieve better results than the existing scheme. Therefore Eurotransplant adapted their proposal and in March 1996 implemented a new kidney allocation scheme (ETKAS). In this new scheme, patients are initially selected based on donor-recipient ABO blood group compatibility (0 to 0+B groups, A to A+AB groups, B to B+AB groups and AB to AB). Following that, patients are prioritised, the highest priority being given to 000 mismatches, followed by high urgency recipients and then the remaining elective patients. All candidates are assigned points on the same five allocation criteria as XCOMB, which were adjusted for the ABO blood group matching and PRA level according to the ET rules. A correction was applied to the distance factor to incorporate the regional and national levels. Paediatric recipients are defined as age <16 years and they receive waiting time bonus according to their age: 3 years bonus for 0-5 years old, 1 year bonus for 6-10 years old and 2 years bonus for 11-15 years old. After an initial 6 months, a further correction was applied. Double HLA mismatch points were assigned for paediatric recipients and higher

points were given to local patients compared with no points assigned for the distance and balance factors for ET non-residents patients (table 1.8).

The new system does not include combined kidney-pancreas and kidney-liver transplants as well as the acceptable mismatches and highly immunised patients, for whom special programs are in place.

Initial results were published in 1998 (119), one year after the implementation of the scheme and were compared with those obtained in 1995. There was no significant change in the number of transplants performed in the two periods and no change in the level of HLA immunization. Important changes were noted in the percentage of long waiting patients who have been transplanted. There was a statistically significant increase in the 2-4 year waiting group and more than a 100% increase in the >5 year group. However this increase did not incorporate highly sensitised patients who are currently not covered by this allocation scheme.

Significant changes were also noted in the matchability profile with more poorly matchable patients being transplanted. Even in subgroup analysis, this positive effect persisted, preventing the accumulation of rare HLA phenotypes or homozygous HLA loci in the long run.

Factor	Points	
HLA mismatch	400	0 mm
	333	1 mm
	266	2 mm
	200	3 mm
	133	4 mm
	66	5 mm
	0	6 mm
Mismatch probability	100	Low
	↓	↓
	0	High
Waiting time	200	Highest
	↓	↓
	0	Lowest
Distance	260/300*	Local
	↓	↓
	208	Regional
	↓	↓
	104	National
	↓	↓
	0	International
National net Import/Export balance	200	Lowest
	↓	↓
	0	Highest
Non-residents*	No points for distance and balance	

Table 1.8 Points system in the new ET kidney allocation scheme. * reflects changes in October 1997

A sensitive issue was the international import-export balance with a fear that Germany, which accounts for 75% of the Eurotransplant waiting list, would continue to maintain a significant import surplus. However, after an initial period of four months, equilibrium of the balance was attained and was maintained throughout the study period, with variations between –20 and +20. Nevertheless, there was a sudden

but transient fall in the activity of some transplant programs in certain countries since maintaining an import-export balance among transplant centres was not one of the main priorities of this patient-oriented allocation scheme.

The new system was found to be easily adaptable for various needs as was demonstrated by the changes made for the paediatric patients and non-residents, which were implemented without affecting the overall balance of the system.

c. *Allocation of organs for transplantation in New Zealand and Australia*

In New Zealand, cadaveric kidneys were traditionally allocated by renal transplant physicians on the basis of local needs and factors known to influence graft survival, in particular HLA matching and the crossmatch results. This approach was not only subjective, but also led to some patients waiting long periods mainly because of an unusual tissue type. Therefore in 1999, a computer-based allocation scheme was developed. In order to enlarge the likelihood of an excellent match, it was even considered that New Zealand would join the Australian Allocation system, but logistic, legal, financial and ischaemic time delays made this impractical.

In the first instance, the New Zealand allocation system (120) now takes into account recipient factors affecting graft outcome (increased age, co-morbid conditions, primary renal disease, previous transplants) to ensure an equitable access to the waiting list for every patient. The level of sensitisation is not a factor *per se*, as it is

believed that the length of time spent on the waiting list will be a good substitute marker for it. The only donor factor taken into account is the age match, as it is considered that in the setting of this country, the cold ischaemic time is unlikely to be a significant issue.

As with all the systems described previously, the New Zealand allocation system has the closeness of HLA matching between the donor and recipient as the prime criterion. The scheme has three ranks (levels) of allocation and points are allocated for rank 1 and 3 independently (table 1.9).

If the total score in rank 1 is less than 58 000, then kidneys will be allocated on rank 2 - if there are any suitable children (humanitarian grounds) or diabetics receiving a simultaneous kidney-pancreas transplant - or rank 3, where consideration is given to the HLA-DR matching, which is deemed more important than Class I matching. The waiting time is taken into account only when two or more recipients have identical scores by HLA matching.

The results of this new allocation scheme have not yet been published.

Rank 1 allocation protocol	**0,1,2 HLA mismatches**
1. Initial score	60 000
2. Deduct for each mismatch	
HLA-A	980
HLA-B	990
HLA-DR	1010
3. Add time for each month*	0.1
Rank 2 allocation protocol	**Children with no potential live donor** **Diabetic patients for SKP transplant**
Rank 3 allocation protocol	**Remainder of the HLA matches**
1. Age	
a. donor<50 / recipient<55	11
b. donor>50/recipient>55	11
2. HLA-DR mismatch	
0	30
1	20
2	10
3. Time points for each month*	0.3

Table 1.9 Points system in the New Zealand kidney allocation scheme. * recipient waiting time

In October 1999, the Transplantation Society of Australia and New Zealand published a revised allocation scheme for cadaveric donor organs in Australia (121). After an initial elimination procedure based on ABO compatibility, HLA antibody specificity, previous transplants with specific mismatched donor HLA Ag and positive lymphocytotoxic crossmatch, the potential recipients are ranked by weighting a number of factors relevant to graft survival. The allocation criteria are weighted in the order shown in table 1.10.

Matching criteria		National score
	Base score	60 000 000
1. **HLA match group**	Deduct for each HLA-DR mm	5 000 000
	Deduct for each HLA-A mm	1 000 000
	Deduct for each HLA-B mm	1 000 000
2. **Sensitisation**	Add for each Pkab>50%	10 000
3. **Waiting time on dialysis**	Add x no. Months dial	100
4. **State exchange balance**	Add x state exchange balance	10
5. **Paediatric bonus**	Add for paediatric patient	30 000

Table 1.10 Points system in the Australian kidney allocation scheme.

There is mandatory exchange of kidneys with 000 HLA mismatches (level 1). Kidneys with 1 HLA-A or B but not DR mismatches (level 2) are exchanged if the balance of exchange is greater than 5 and the recipient has greater than 50% peak PRA and a negative crossmatch, while kidneys with 2 HLA-A or B but not DR mismatches (level 3) are shared if the exchange balance is greater than 10. Each Australian state has its own allocation policy for kidneys that do not fall in the best-matched groups (level 3 patients, who score less than 58000000 on the national HLA matching scheme). These schemes are also based on the HLA mismatches but take into account a variety of other factors (waiting time on dialysis, medical urgency, recipient fitness, donor-recipient CMV status).

The new Australian allocation protocol was introduced in October 1999 and results are yet to be published.

d. Allocation of organs for transplantation in the United Kingdom

On the first of July 1999, after extensive computer modelling, the United Kingdom Transplant (UKT) special authority introduced a new allocation scheme (17). This scheme acknowledged the degree of HLA matching as the main factor of the distribution system and assigned the potential recipients in three groups. Full match (000 mismatch) represent Tier 1 group, those with other favourable matches (100, 010, 110, 200, 020) form the Tier 2 group, while the unfavourable matches are grouped under the Tier 3 heading. Priority is given to local patients versus national ones and to highly sensitised patients (PRA>60%). Both adult and paediatric organs are initially offered to paediatric recipients (table 1.11).

Adult organs				**Paediatric organs**			
Tier 1	Child	HSP	Local	Children	Tier 1	HSP	Local
			National				National
	Child	Non-HSP	Local			Non-HSP	Local
			National				National
	Adult	HSP	Local		Tier 2		Local
			National				National
	Adult	Non-HSP	Local		Tier 3		Local
			National				National
Tier 2	Child		Local	Adults	As for children		
			National				
	Adult		Local				
			National				
Tier 3			Local				
			National				

Table 1.11 New UK kidney allocation scheme priority order. (HSP= highly sensitised patient)

A points system is used if more than one patient satisfies the initial criteria. Points are allocated for the length of waiting time, for the degree of sensitisation, for the recipient age and donor-recipient age difference and for the centre balance of exchange (table 1.12).

Criteria	Criteria range	Points	Aim
Recipient age	Old to young	1 – 10 points	Favours younger recipients
Donor/Recipient Age Difference	Large to small	1 – 10 points	Avoids large age difference
Waiting time	Short to long	0.5 – 5 points	Favours longest waiting
Matchability	Easy to hard	1 –10 points	Favours rarer HLA types
Sensitisation	High to low	0.5 – 3.5 points	Favours low sensitisation Avoids +ve cross matches
Balance of exchange	Low to high	1 – 10 points	Favours higher centre balance

Table 1.12 Points scoring mechanism used by the UK donor organ sharing scheme.

The initial results were presented at the British Transplantation Society meeting in March 2000. There was a 9% increase in the number of fully or favourably matched adult transplants compared with the previous year. This was associated with an 18% increase in organ exchange among the transplant centres. A 14% increase in Tier 1 and 2 transplants was observed in the paediatric group, where 26% more organs were exchanged. This change was not associated with a significant increase in the length of the cold ischaemic time, but there was a small statistically significant difference

(p=0.03) between local transplants and imported organs. The report also highlighted that there was no significant effect of points scoring factors and no change in the age distribution of the transplanted patients. As a result of this analysis, two improvements to the scheme were introduced. The first one was a prioritisation of HLA-DR homozygous patients for HLA-DR homozygous donor kidneys and the second one was the initial offering of the second adult kidneys to national paediatric recipients before locally matched adults.

A two-year analysis (122) confirmed that HLA matching improved significantly for adults and children and for both first and re-graft recipients. There has been a three fold increase in the number of HSP 000 mismatch grafts, donor-recipient age differences have decreased and the matchability point scoring seems to have the desired effect of transplanting more patients who are difficult to HLA match. However, it was noted that the adults transplanted through this new scheme are younger than previously, and therefore further monitoring is required to investigate whether there is a bias towards younger patients.

e. *Regional alliances and allocation of organs for transplantation in Scotland*

A significant development in the allocation of organs in UK was the creation of regional sharing alliances. The purpose of these alliances was to optimise the local use of kidneys, increasing the sharing of well matched organs with a minimal impact on the length of cold ischaemic time. The alliances have a unified waiting list and act

as a single organisation in the exchange of kidneys with the national pool managed by UKT. They represent an additional kidney sharing level, participating centres exchanging well matched kidneys at this regional level, before offering them to the national organisation. At the moment there are 6 regional alliances in UK (table 1.13) and only three of them have a scoring system based on the national scheme.

Regional alliance	**Point scoring system**
North Thames	Lacks a point scheme
South Thames	Lacks a point scheme
Scotland-Northern Ireland	Based on the national scoring system
North of England	Own scoring system
Trent	Based on the national scoring system
South-Western Wales	Based on the national scoring system

Table 1.13 Regional alliances in UK and local points scoring systems

In April 1997, Aberdeen, Dundee and Edinburgh formed an alliance in the South-East of Scotland. This was prompted by several reasons. Firstly, there was evidence suggesting that in the current era of modern immunosuppression, matching for anything less than a full house match (000 mismatch) had little impact on outcome and therefore placing the kidney with a slightly poorer matched recipient, but with a shorter cold ischaemic time, may produce a good outcome. Secondly, South East of Scotland had a highly positive balance of exchange with the national pool. Thirdly, a major determinant as to the fate of the kidney is in the size of the waiting list in a particular area, and therefore the alliance would ensure a better distribution of locally retrieved as well as UK shared kidneys.

The alliance had its own internal scoring system based on HLA matching, length of time on the waiting list and recipient age. At least one of the kidneys retrieved locally was retained within the alliance (both if there was a significant positive balance of exchange with UKT) and offered sequentially to patients from the unified waiting list, ranked in order of their points scoring. The alliance functioned in this format until 1st of September 1999, when Glasgow and Northern Ireland joined in to form the Scotland-Northern Ireland Alliance. The start date allowed for the new National Allocation Scheme to be implemented and used as a base for the new alliance's activity. The regional scheme applies to kidneys identified within the alliance, which are initially offered to the participating centres before being offered nationally. All kidneys retained locally are allocated according to the national Tier 1 and Tier 2 criteria set in table 1.11, while for Tier 3, kidneys are first offered to HSP (>85% PRA) patients. In the event of ties, waiting time is used as a factor, but the ultimate discriminator is the distance between the retrieval and transplant centre.
Since the introduction of the Alliance, there have been two changes in the sharing protocol, first to incorporate the offering of kidneys with cold ischaemic time in excess of 20 hours back to the retrieval centre into their local scheme and second to permit blood group compatible matches for well HLA matched children.

In summary, most organ sharing networks throughout the world allocate cadaveric kidneys in a similar manner, although the exact scoring systems vary. Despite the continuous debate, HLA matching remains the main allocation criteria in most systems, but other significant factors (waiting time, sensitisation, age, geography) are given the appropriate weight in order to make a system equitable and useful.

Allocation algorithms must be dynamic and allow for changes in population demographics as well as the social and ethical needs of a particular society. Nevertheless, one has to bear in mind that any allocation policy deals only with the last step in the pathway to transplantation and to reach this stage, a patient must have access to a renal replacement centre, be referred and have a thorough assessment and finally listed, if considered suitable for transplantation.

1.6 ACCESS TO TRANSPLANTATION

Access to transplantation is a very important topic for the renal patient and the transplant community. Despite general agreement on surgical technique, organ preservation, transplant immunology and immunosuppression, the way we select patients onto the renal transplant waiting list is still subject to wide debate.

With the current shortage of donor organs, it is inevitable that some groups of patients will be discriminated against in gaining access to transplantation (123-126) and despite the philosophical arguments, this is widely regarded as unacceptable.

Several studies have confirmed that gender-based disparities documented in the use of other medical services, such as cancer-screening tests (127), cardiovascular procedures (128) and treatment for HIV (129), also exist in access to the renal transplant waiting list and renal transplantation (124-126;130-132).

It has been argued that the higher proportion of men that are transplanted is simply due to their increased requirement of renal replacement therapy and there is no evidence of unintentional discrimination (133). Most authors would now agree that although this is a genuine observation, it is a rather simplistic explanation. It has been hypothesized that differences in health and socio-economic status may be partly responsible (123;124;134), but these factors, although reducing the magnitude of the disparity when taken into account, do not fully explain the lower listing and transplant rates noted among female patients (130;135). Several investigations have shown that men and women are referred at similar stages of renal failure (136) and the incidence of non-compliance or psychiatric illness is similar in both genders (137) and hence do not stand as pertinent explanation for these differences. In

addition, concerns about outcome after transplantation are not likely to be explanatory as patient and graft survival are comparable for both genders (21;138;139). Some have speculated that a few of the gender-based differences, in particular the longer waiting time for a transplant after listing may be a result of differences in antibody status between men and women (124). Little is known about gender differences in patient or family preferences for transplantation and although studies have not shown a lesser preference for transplantation among women (140), there is scope for further research on this subject. Finally, the possibility of a gender bias by health care providers has been demonstrated for other medical therapies (141) and raised in transplantation by a study indicating that women are less likely to be identified as potential transplant candidates by renal unit staff (131). Although a specific cause for gender differences has not yet been identified, undoubtedly, the explanation is complex and most of the above factors have an intrinsic role. It is likely that variables which are difficult to quantify or insufficiently explored (such as patient preferences, attitudes and beliefs, the role of education and employment status and the provider bias), rather than biologic and clinical differences are responsible for the reduced access to transplantation for female patients.

Even greater differences in access to health services were reported according to the patient's race (128;141). Ethnic minorities, and in particular those of African origin have a significantly higher risk of renal disease (142), which is doubled by a lower chance of being listed for transplantation and receiving a kidney transplant compared with white patients (123;126;132;143). These differences have been documented for over a decade and several explanations have been advanced. Some of the reasons lie with the socio-economic and educational disadvantages often encountered by these

patients (144), but even after a fully informed choice of the treatment options and a clear preference for transplantation (145), further access to a kidney graft is much slower than for white patients (146). It has been argued that racial disparities reflect underlying clinical differences, as black patients are more difficult to match and are more likely to have a positive crossmatch than similar white recipients, precluding transplantation from a given donor (147). In addition, due to various non-immunologic (more uncontrolled hypertension, higher rate of non-compliance) and immunologic (higher incidence of delayed graft function and acute rejection episodes) factors, transplant results are poorer in black recipients (148).

Other factors such as subconscious bias or financial disincentives for the health care providers as well as regional variations in the matching algorithm may also play a role (123;148), but require further study. The lower transplant rates observed in certain ethnic minorities have been linked with the lack of suitably matched donor organs. This is partly due to lower donation rates among these groups which may be explained by cultural problems with brain stem death (BSD) diagnosis rather than religious constraints (as most religions have accepted BSD). Several initiatives to increase donation rates in these ethnic groups and allow more patients to be transplanted have been proved to be successful (149).

Many transplant centres are reluctant to accept elderly patients on their waiting lists (125), as they are frail, have a higher comorbidity index (150) and a lower life expectancy. An increased age has a significant impact on long-term graft survival and more than 40% of the grafts in elderly recipients are lost due to patient's death (150;151). In the current shortage of organs this has been viewed by many as a waste of organs which could otherwise be suitable to younger patients. Nevertheless, as the

number of elderly requiring RRT is progressively increasing and the evidence of transplantation being a safe and successful procedure is mounting (152;153), the attitude towards the age criteria has been revisited. Nowadays it is largely agreed that age *per se* does not represent a contraindication to transplantation and a careful evaluation of the older candidate and tailored post-transplant management may allow for further expansion of indications for grafting in this particular age group.

Similarly, there are differences in access to transplantation according to the primary renal disease. In particular diabetic patients are markedly disadvantaged both for listing and transplantation (143). It has been argued that these patients have a higher comorbidity index pre-listing, associated with an increased risk of developing further complications once listed, which precludes them from being a transplant recipient.

A low income has been shown to reduce the likelihood of completing the transplantation process (123). Although the transplant outcome is not influenced by poverty (154), it has been suggested that these patients have an overall poorer access to health care, are more non-compliant and are less likely to appreciate the advantages of transplantation. Therefore, they may not be good advocates for themselves when it comes to choosing the best treatment option (146).

It is not surprising that patients with certain comorbid conditions have a lower access to transplantation, but unfortunately, this is not the sole explanation of the substantial differences in access noted for various age, gender, race and socio-economic groups. In addition to the factors already mentioned, other issues such as religion, fear, lack of knowledge my be responsible for some of the differences noted at different stages of the transplantation process.

The identification of these potential barriers on the way to transplantation will allow a more focused research into ways to overcome their causes as well as producing standardized listing criteria which could be an important step towards correcting some of the disproportions noted in the current system of access to renal transplantation.

1.7 ASSESSMENT FOR TRANSPLANTATION

The assessment process is an important stage which will ensure that a patient is fit to undergo transplantation. This process must not be used as a cloaking device to exclude patients on the grounds of age, race, gender or other demographic or socio-economic factor. It should rather be an evidence-based process, which assesses the risk of each comorbid condition exhibited by individual patients and provides useful information regarding the operative risk and the chances of a successful long-term outcome. At the end of this process, the patient should be advised about the risks and benefits of transplantation and a decision regarding the best therapeutic approach to follow should be reached.

Each transplant candidate is unique and faces distinct clinical and psycho-social challenges and therefore it is not possible to design a comprehensive assessment process to meet the needs of every single patient. On the other hand, the large amount of often conflicting information relating to the evaluation of a transplant candidate has lead to significant practice variations (155;156) and highlighted the need for a standardized approach and universally accepted listing criteria. Some clinical practice guidelines have been issued, in an intent to address some of these differences (18;157).

As we are getting better in managing difficult cases and as the demographics of the RRT population are rapidly changing, the assessment process is likely to evolve to

allow an increased number of patients with complex medical history to be accepted for transplantation. Therefore any set of guidelines must be reviewed and updated on a regular basis to keep pace with these changes.

The fundamental role of the assessment process is to identify the comorbid diseases which are likely to adversely affect the outcome and to determine whether the risk factors will render transplantation less effective than dialysis. Once the need for transplantation has been established and the patients have indicated their willingness for transplantation, they should undergo a detailed clinical evaluation (figure 1.13).

The presence of a cancer must be ruled out as it is generally accepted that immunosuppressive therapy increases the aggressive nature of any tumour. A waiting period between the cancer treatment and transplantation longer than 5 years would exclude 87% of the patients who would develop a recurrence, but this may not be practical in elderly candidates where shorter waiting times (*e.g.* 2 year waiting time eliminates 53% of recurrences) may be more appropriate (158).

Patients should be screened for the presence of overt or occult infections (urinary tract infections, dental caries, dialysis access sites, tuberculosis) and any focus should be eradicated prior to acceptance onto the waiting list. At present, HIV is an absolute contraindication to transplantation because most of the HIV positive patients undergoing transplantation have fared badly (159). The viral status of the patient, in particular CMV and EBV viruses, should be determined as effective prophylaxis is required in positive cases to reduce the risk of serious comorbidity and graft loss (160).

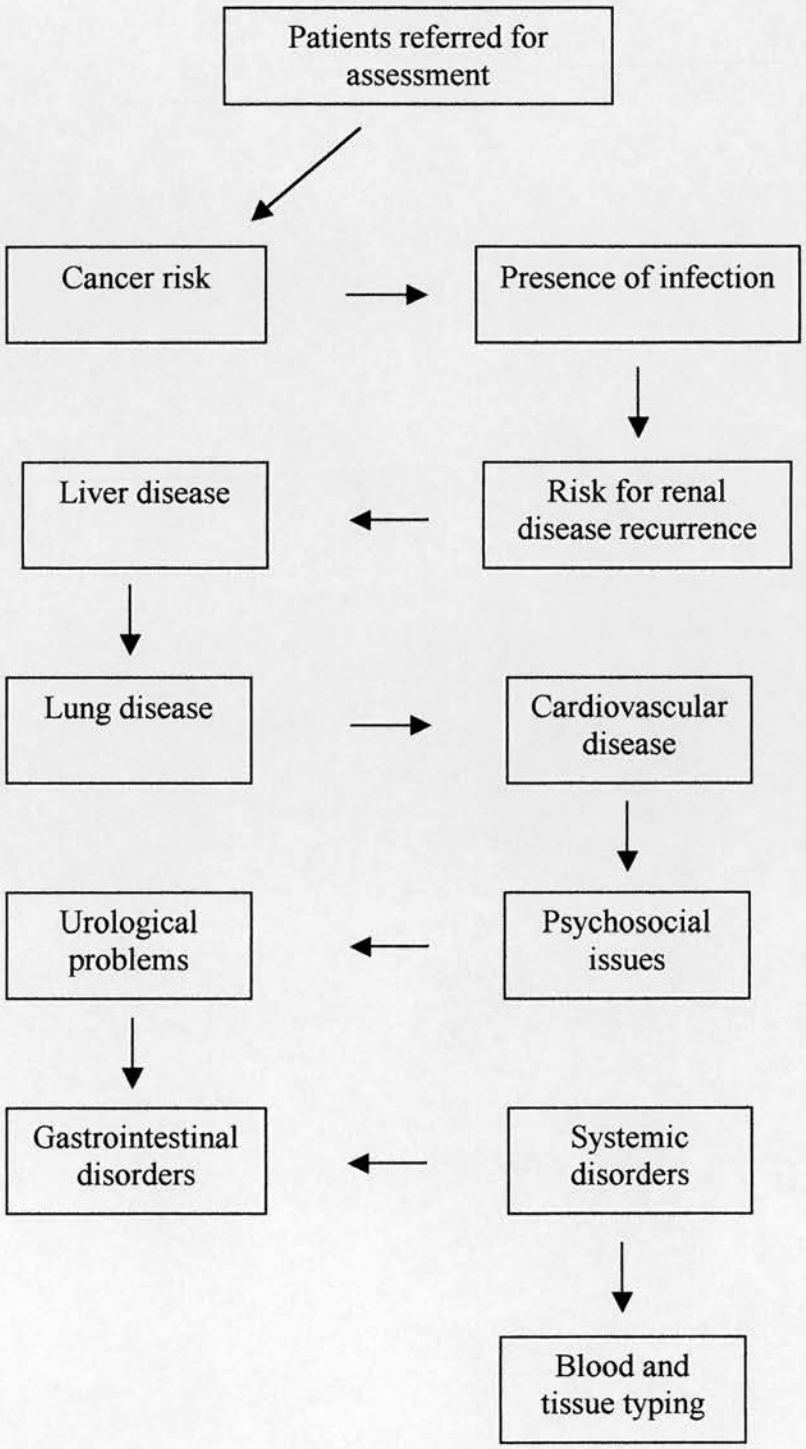


Figure 1.13 Overview of the assessment algorithm (adapted from (18))

Patients suffering from certain renal diseases such as Wegener's granulomatosis, focal segmental glomerulonephritis, IgA nephropathy, type I membrano-proliferative glomerulonephritis, to mention just a few, have a well defined risk of disease recurrence in the transplanted kidney which can be as high as 50%. These patients must be advised of the risks and if transplantation is unlikely to produce a significant benefit over dialysis. The decision whether listing is appropriate should involve the patient and the whole transplant team.

Symptoms and/or liver enzymes abnormalities should prompt further investigation. There is controversy surrounding the need for pre-transplant cholecystectomy, but with an increased risk of life-threatening cholecystitis after transplantation (161) it may be prudent to recommend that diabetics with gallstones or patients with persistent symptoms should be considered for surgery prior to transplantation. Similar controversies surround patients with positive hepatitis viruses. There is some evidence to suggest that both hepatitis B (162) and hepatitis C (163) patients are at increased risk of dying in the post-transplant period, but the exact risk has not yet been determined, and therefore transplantation is generally recommended in these patients. However, patients with evidence of active viral replication or patients who are hepatitis delta positive may best decide against transplantation as they are at very high risk of disease progression (164).

There is little information about assessment for patient with respiratory diseases (other than pulmonary infections) but the same principles for the preoperative evaluation as for any other type of surgery would apply (165). There is general agreement that patients with controlled asthma or chronic obstructive pulmonary

disease can be transplanted, while smoking increases the risk of surgery as well as the risk of cardiovascular diseases (166) and graft failure (167).

Cardiovascular diseases including acute myocardial infarction, cardiac arrhythmias, heart failure, cardiomyopathy and stroke are the leading cause of death following transplantation, accounting for over 50% of death in these patients (168). Mortality rates from coronary disease for transplant recipients are 25-fold greater than that of an age and gender matched population (169). Furthermore, the risk of cardiovascular events is not just a result of the early post-transplant events, but tends to accumulate over time. Previous studies have identified several risk factors including age, diabetes, hypertension, hypercholesterolaemia and cigarette smoking (170) as well as pre-existing diseases including coronary heart disease, peripheral vascular disease and cerebrovascular disease (168;171). The identification of the risk factors as well as pre-existing diseases allows for a risk stratification of the prospective transplant recipients and for more complex investigations such as isotope myocardial perfusion scanning or dobutamine echography, coronary angiography and intracoronary ultrasound to be performed only in those considered at high risk (172). In addition, the identification of pre-transplant cardiac diseases and risk factors allows for timely risk modification intervention strategies, which could lead to a successful management of the cardiovascular risk and prolongation of patient and allograft life (173). The use of ACE inhibitors to lower the blood pressure, of statins to lower the lipid levels, glucose control, aspirin prophylaxis and smoking cessation may favourably influence the incidence of cardiovascular diseases (174;175). Despite an increased risk of cardiac surgical procedures in renal failure patients (176), it has been suggested that patients with critical coronary lesions should undergo

revascularization (angioplasty, stenting, by-pass surgery) prior to transplantation (177), as it leads to a lower post-transplant risk of cardiovascular events.

There is an increased risk of cerebral vascular disease after renal transplantation (170) and patients who already have a history of cerebrovascular disease should be advised and the risk factors should be addressed. Patients with transient ischaemic attacks or other evidence of cerebral vascular disease should be referred for neurological assessment and treatment and transplantation should be undertaken only after a minimum symptom free period of six months (18). There is no evidence to suggest that screening renal transplant candidates with asymptomatic carotid bruits for cerebral vascular disease is beneficial and no firm recommendations have been made so far for their management.

The incidence of peripheral vascular disease (PVD) in renal transplant candidates is high (18;178), but the evidence analysing the impact on clinical outcome is scarce (179). Peripheral vascular disease, and in particular aortoiliac disease can pose significant technical problems and therefore symptomatic PVD should be investigated by a pretransplant angiogram and surgical reconstruction carried out before or even at the time of transplantation (180).

Psychological and social issues are very important in transplantation. A patient should be able to give an informed consent for the procedure and must have the capacity to adhere to the strict post-transplant medication regimen. The assessment procedure will identify issues such as personality disorders, psychosis, substance dependence or abuse, which are likely to affect compliance (181;182) and patients should be referred for evaluation and treatment prior to listing. It is generally

accepted that appropriate psychiatric treatment can and should eliminate the barriers to transplantation in this group of patients (181).

Particular attention in the assessment process must be paid to those patients who have developed renal failure due to urinary tract problems. A comprehensive genito-urinary work-up (ultrasonography, voiding cystourethrogram, cystoscopy, retrograde pyelograms) and urological expertise are necessary in these patients to ensure the problem will no longer be present to damage the transplanted kidney (183).

Gastrointestinal diseases present in a transplant candidate should be documented at the assessment clinic, as they can complicate the post-transplant course. Colonic complications occur in about 2% of the transplanted patients, but screening should be reserved only for those with previous episodes of active diverticular disease or inflammatory bowel disease (18). It is important to mention that there is no demonstrable increase in the risk of colon cancer after transplantation, but there is insufficient data for those already at risk, such as ulcerative colitis patients. Many studies have demonstrated an increased incidence of peptic ulcer disease in the renal failure population (18-40%) with a significant impact on the comorbidity in the post-transplant period. This has prompted some centres to advocate the routine use of H2 receptor blocker treatment and surveillance endoscopy (184). Little data is available for the impact of pre-transplant pancreatitis, but any reasonable cause should be ruled out during the assessment process, as a relapse post-transplantation is often associated with high morbidity and mortality (185).

Obesity is a well-defined risk factor for post-transplantation morbidity and a body mass index (BMI) of less than 30 has been suggested by some as a prerequisite for placement on the waiting list (186). Secondary hyperparathyroidism, particularly if

symptomatic, should be treated surgically prior to admission onto the waiting list (18).

Advanced age and diabetes pose a higher risk for transplant failure and in these groups of patients, the threshold for investigations for all of the conditions highlighted above should be low. Eligibility for transplantation should be judged on the overall clinical condition of the patient and not based solely on the belonging to a particular high-risk group.

Once the assessment process is completed, several blood and tissue typing tests should be carried out to determine the compatibility of the recipient with a potential donor and to ensure that the candidate is immunologically acceptable for the waiting list.

The assessment process may be long and time-consuming, but addressing all the issues highlighted in this synopsis will ensure a successful listing and a better outcome for the patient and the renal allograft.

SUMMARY AND AIMS OF THE STUDY

Transplantation has seen a huge progress during the last three decades. Despite that, the service is under tremendous pressure due to increasing demand but a limited supply of donor organs. This has highlighted, yet again, a series of controversial issues concerning organ allocation, equity of access, standards of the assessment process and appropriateness of transplantation in certain groups of patients.

There is virtually no data on these issues in the Scottish renal transplant setting and therefore the aims of this thesis are to provide a comprehensive picture of the current status of the service and to identify areas where improvements are required to make it more accessible and successful. Consequently, this thesis aims to answer the following questions:

1. What are the benefits of the current allocation schemes and the influence of the new regional Scotland – Northern Ireland Alliance on the transplant activity?

2. Is there equity of access to the transplantation service? If not, which are the sociodemographic and comorbidity factors which may be responsible for these differences?

3. Does transplantation provide a survival advantage over dialysis in various renal failure subpopulations? Is there any benefit in transplanting high-risk groups of patients?

4. Are there any differences in the assessment process? Can the risk factors identified at the assessment process be quantified into a patient survival risk score?

CHAPTER 2

ALLOCATION OF KIDNEYS IN SCOTLAND AND SCOTLAND-NORTHERN IRELAND ALLIANCE

2.1 INTRODUCTION

The success of transplantation as a form of treatment for end-stage renal disease has contributed to increasing numbers of patients on the waiting list. As has been demonstrated, this increase over the years has been exacerbated by a fall in the number of available cadaveric kidneys. The shortage of organs has prompted the need for improved allocation schemes and the new systems, which have been implemented worldwide, showed encouraging results (110;187).

On the 1st of July 1998, after a multifactorial analysis and computer modelling, the national transplant authority (UK Transplant) introduced a new allocation scheme in the United Kingdom (17). The new scheme allocates adult cadaveric donor kidneys to ABO identical recipients based on three tiers of HLA matching (table 2.1).

	Full house match	Favourable matches	Non favourable matches
Identification	Tier 1	Tier 2	Tier 3
Definition	No HLA mismatches	One mismatch for HLA-A and/or HLA-B and no mismatches for HLA-DR	One or two HLA-DR mismatches and/or two mismatches for HLA-A and/or HLA-B
Mismatches	000	100,010,110	All other matches

Table 2.1 Levels of mismatches for the UK donor organ sharing scheme.

At each level priority is given to paediatric over adult, highly sensitised (PRA ≥ 85%) over non-sensitised, local over national recipients respectively. In Tier 1 both kidneys are offered to patients with 000 HLA mismatches (if two such patients exist), while in Tier 2 only one kidney will be made available for national allocation when there are no patients (or one patient only) in either Tier 1 or Tier 2 on the local list. Tier 3 kidneys may be retained for local use, but if no suitable recipient is found, they are offered nationally through UKT to the unit with the highest balance of exchange. When two or more equally matched patients are identified for any kidney, a points scoring mechanism is used as a discriminator to determine the recipient (table 2.2).

Criteria	Criteria range	Points	Aim
Recipient age	Old to young	1 – 10 points	Favours younger recipients
Donor/Recipient Age Difference	Large to small	1 – 10 points	Avoids large age difference
Waiting time	Short to long	0.5 – 5 points	Favours longest waiting
Matchability	Easy to hard	1 –10 points	Favours rarer HLA types
Sensitisation	High to low	0.5 – 3.5 points	Favours low sensitisation
Balance of exchange	Low to high	1 – 10 points	Favours higher centre balance

Table 2.2 Points scoring mechanism used by the UK donor organ sharing scheme.

In case of a tie between patients following the points score, the shorter transport time between the retrieval and recipient centre will be used to make the final decision. The introduction of this new donor organ sharing scheme has encouraged more centres to join or create new sharing alliances in an attempt to optimise regional waiting lists, organ procurement activity and distribution, decrease ischaemia time and improve the access to transplantation.

A recent analysis of the first two years of this new scheme (188) suggested that the aims of improving exchange rates of favourable matched kidneys between centres, reducing the waiting time on the waiting list for difficult to match recipients and ensuring fair access to the service have been achieved. However this analysis does not take into account the fact that in UK there are several regional alliances, which may produce significant variations in the transplant activity at a regional level. Furthermore, some of them do not use the national sharing criteria in allocating cadaveric organs and hence a pooled national analysis may not reflect the true magnitude of the changes for a particular area.

The new Scotland-Northern Ireland alliance is one of 7 regional kidney sharing alliances existing in UK in 2001. The alliance was formed in August 1998, unifying the activity of the former East Scotland Alliance, which included Edinburgh, Dundee and Aberdeen with that of Glasgow and Belfast. In November 1999, the Dundee unit merged with Edinburgh, so that the alliance has four centres with a catchment population of 6.6 million. The alliance territory is divided into four retrieval zones covered by the participating transplant centres – Aberdeen and Edinburgh for the

East of Scotland, Glasgow for the West of Scotland and Belfast for Northern Ireland. Kidneys may be procured in non-transplanting hospitals by a transplant team from the regional centre and are counted towards the balance of exchange of that centre. All donor organs are allocated through the standard national allocation system, described earlier, and run by United Kingdom Transplant (UKT). For all imports and exports of cadaveric kidneys the alliance acts as a single organisation with a single transplant waiting list.

One of the main concerns within the new established alliances was the potential imbalance of activity, which could arise due to the different sizes of the participating centres. This is one of the main reasons why many UK centres have opted to stay out of regional alliances. The Scotland-Northern Ireland alliance unifies the activity of two small centres - Aberdeen and Dundee (performing less than 25 transplants per year), two medium size centres - Edinburgh and Belfast (25 to 50 transplants per year) and one large centre - Glasgow (more than 50 transplants per year) and therefore represents an ideal model to investigate this issue.

We were interested to analyse the results of the new alliance and to investigate:

1. Whether there is an increase in the number of very well matched kidney transplants
2. The effect of a regional sharing alliance on the length of cold ischaemic time
3. Whether there are any positive or negative effects on the activity of a large transplant centre
4. Whether there are any positive or negative effects on the activity of a small transplant centre

2.2 METHODS

Data regarding the activity of the alliance is collected prospectively, at the moment of retrieval and allocation and stored in a computerised database at UKT. An analysis was carried out for the first two years of activity (1st of September 1998 to 31st of August 1999 and 1st of September 1999 to 31st of August 2000) and compared with the results of the last pre-alliance year data (1st of September 1997 to 31st of August 1998). Prior to September 1998, all kidneys were exchanged through the national system, and not directly between centres. In order to perform a meaningful comparison and to illustrate the impact of forming a regional alliance on the balance of exchange, all kidneys shared between centres in the pre-alliance period were counted towards an "alliance internal balance of exchange". In other words, the four centres were considered as part of an alliance, although technically the organ sharing activity took place through the United Kingdom Transplant.

Information regarding retrieval and transplant activity, the internal balance of exchange, the balance of exchange with UKT, the degree of HLA matching, the number of kidney offers and their outcome as well as the cold ischaemic time (CIT) and graft survival were analysed.

Chi square, unpaired sample Student-t test, Fisher exact test and Log rank test were used to estimate the statistical significance of any differences. All statistical analyses were done with the SAS software package (version 9).

2.3 RESULTS

An overview of the activity for the three year period is given below.

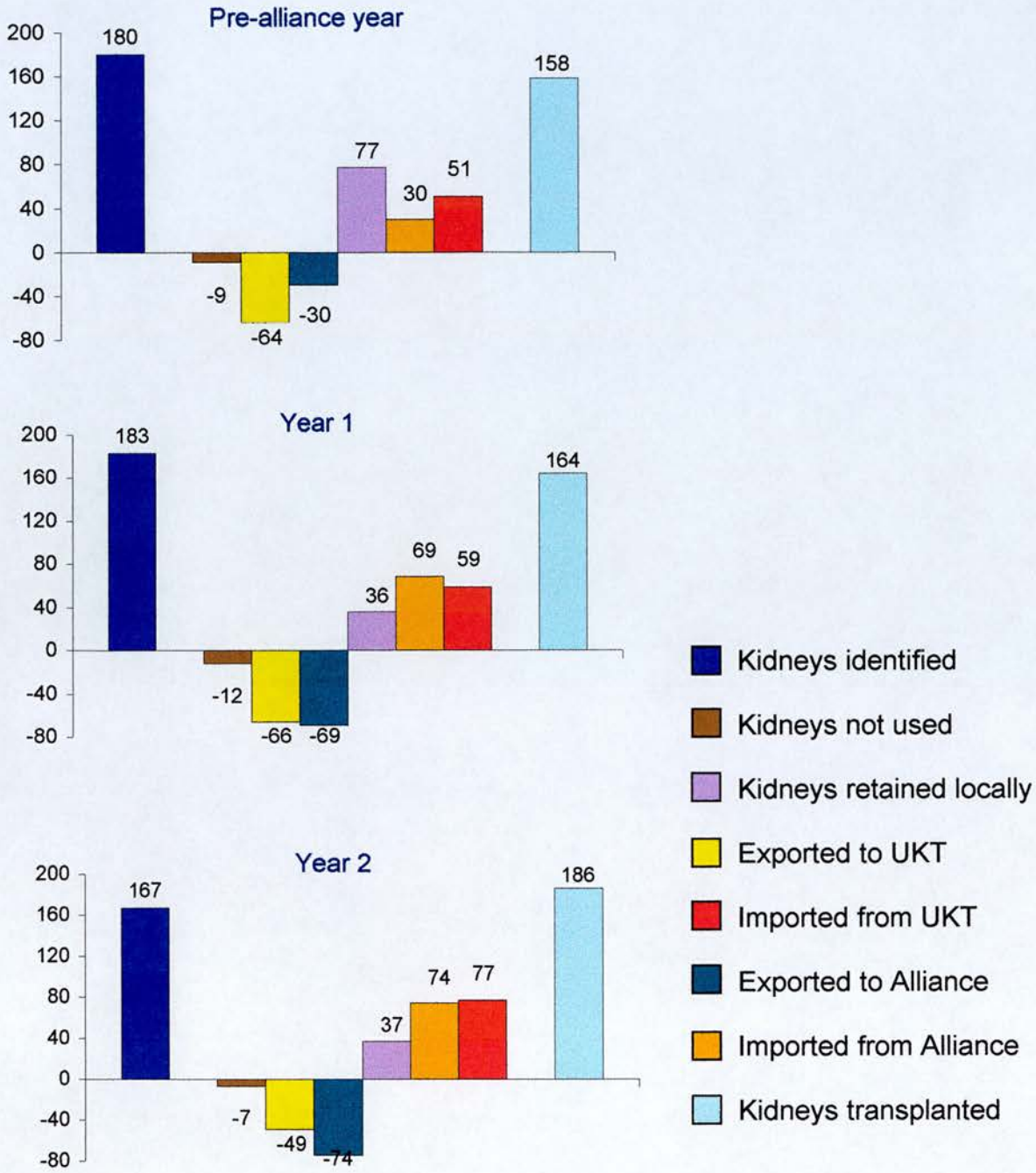


Figure 2.1 Overview of the Scotland-Northern Ireland alliances' activity for the three year period (1.09.1997 – 31.08.1998, 1.09.1998 – 31.08.1999 and 1.09.1999 – 31.08.2000)

2.3.a Retrieval and transplant activity

The population of the alliance has been stable throughout the study period, around 6.61 million people (table 2.3). 183 donor kidneys were identified as being potentially suitable for transplantation in the first year of the alliance (1st of September 1998 and 31st of August 1999), giving an average of 13.9 donors per million population (pmp), slightly above the UK average for the same period (13 donors pmp). This level of activity was similar to the pre-alliance year, when 180 kidneys were identified (13.6 donors pmp). Only 167 kidneys were identified in the second year (12.8 donors pmp) and this decrease mirrored the national reduction in donation rates.

Year	Population (millions)	Number kidneys identified	Number of donors (pmp)	Number of transplants performed
Pre-alliance year	6.61	180	90 (13.6)	158
Year 1	6.61	183	92 (13.9)	164
Year 2	6.61	167	85 (12.8)	186

Table 2.3 Alliance's population (millions), number of kidneys retrieved, number of donors per million population and number of transplants performed in the first two years of activity and the previous year.

There are significant centre variations in retrieval activity over the three-year period as shown in figure 2.2.

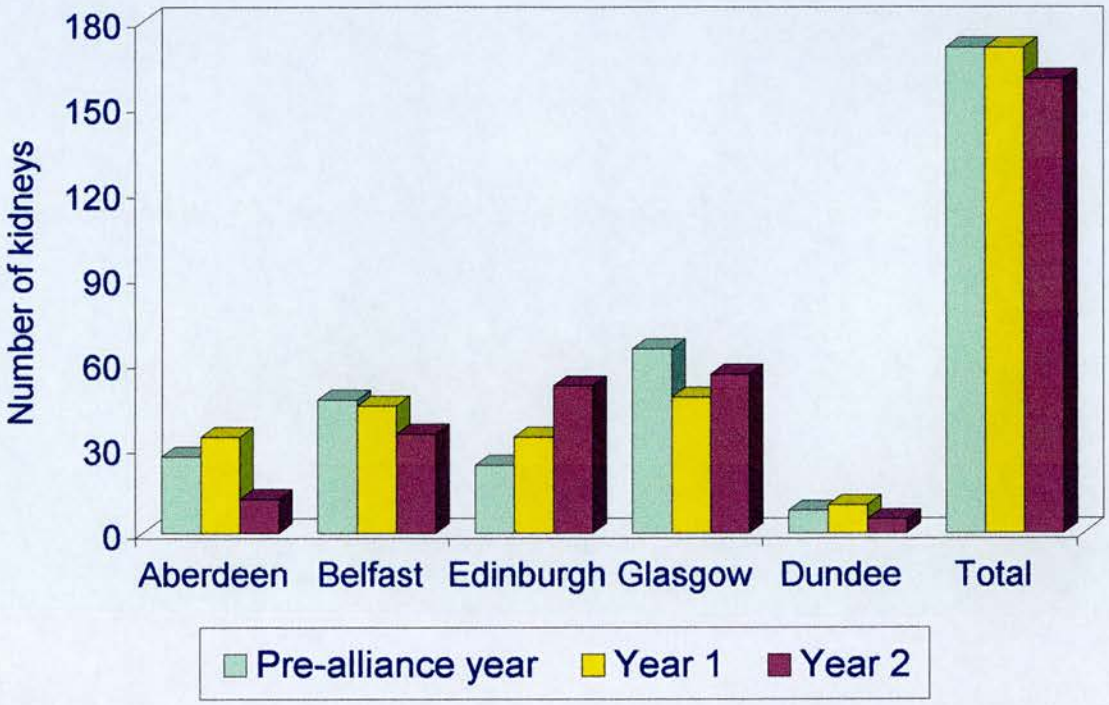


Figure 2.2 Retrieval activity for the alliance and each centre over the three year period

The donations rates ranged between 7.5 pmp in Dundee in alliance's second year of activity and 26.7 pmp (twice the national rate) in Aberdeen in the first year of the alliance. Detailed data for each period and centre are shown in the appendix, table A.7.a-c, page 334.

While the retrieval activity decreased, over the two-year period there was an 11% increase in the transplant activity (figure 2.3).

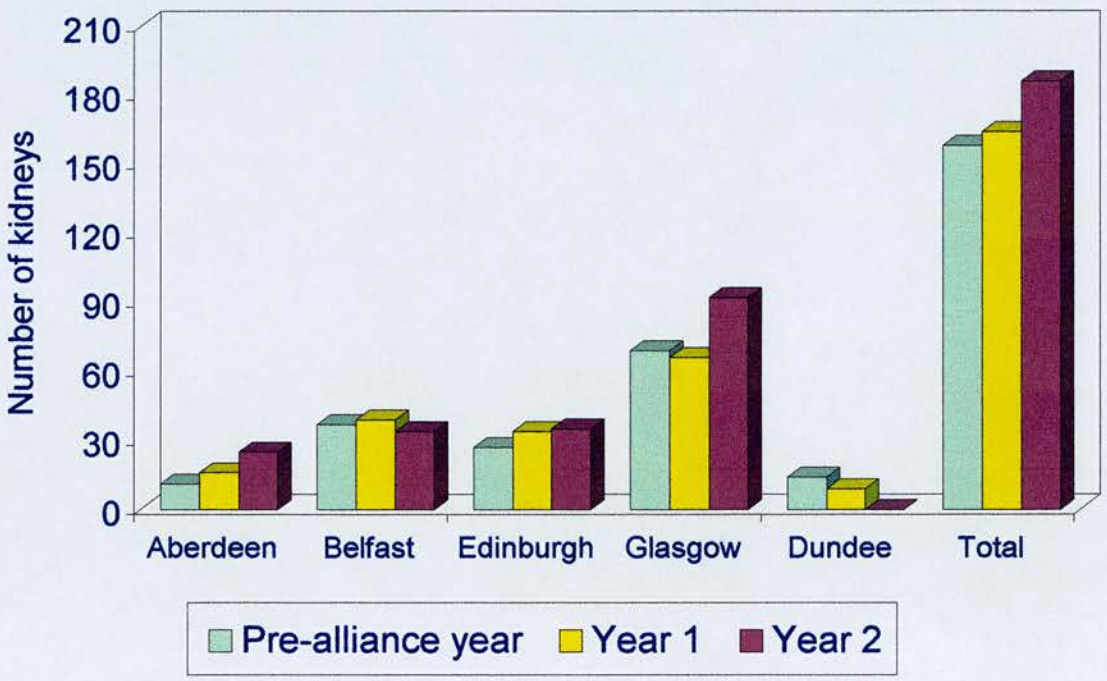


Figure 2.3 Transplant activity for the alliance and each centre over the three year period

The highest increase was noted in Aberdeen (the smallest centre) where the number of transplants doubled (21 compared with 11). A 40% increase in the number of transplants performed was noted for the largest centre (Glasgow) in the second year of the alliance, mainly due to kidneys imported from UKT. Detailed information on

the transplant activity for each centre are shown in the appendix, table A.7.a-c, page 334.

The destination of the retrieved kidneys is illustrated in figure 2.4. With the introduction of the new alliance, there was a significant increase in organ exchange ($p=0.0001$, χ^2). 135 kidneys (79%) have been shipped out of the retrieving centre in the first year, 69 being used within the alliance and 66 exported to UKT, while in the second year, 123 kidneys (77%) were shipped out, 74 within the alliance and 49 to UKT.

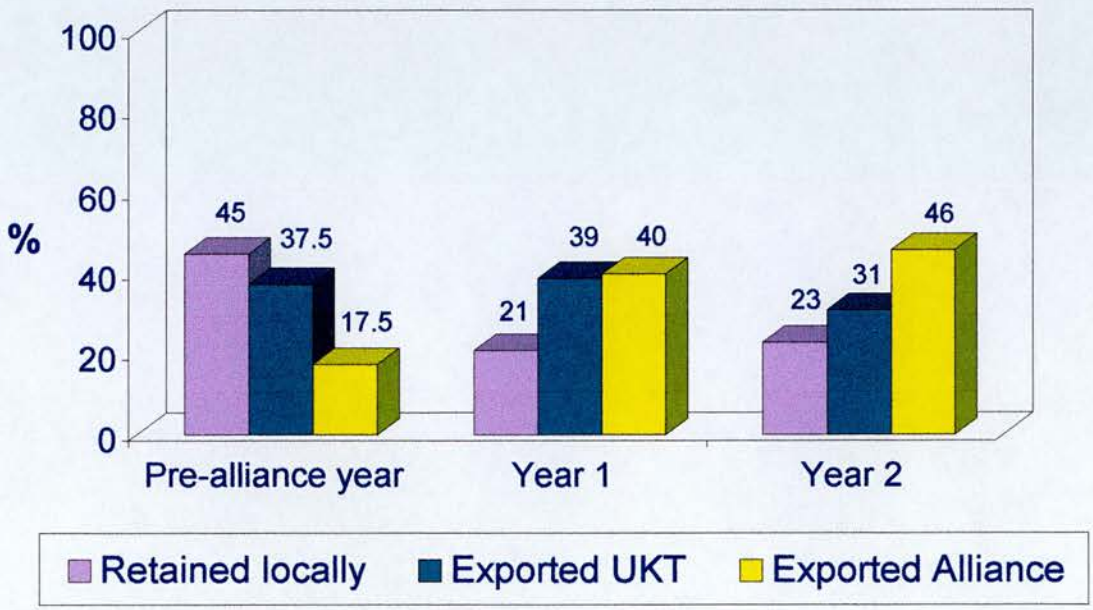


Figure 2.4 Destination of kidneys retrieved in each of the three year period

As expected, there are significant centre variations (table A.8.a-c, appendix, page 335). In the pre-alliance year, Dundee, the smallest centre, exported all retrieved kidneys, while Glasgow, the largest centre, retained 67% of the organs retrieved. The remaining centres retained between 18% and 44% of the kidneys harvested. Although the introduction of the alliance has altered these proportions significantly, (table A.8.b-c, appendix, page 335) the largest centre still retained nearly 45% of the organs retrieved, in contrast with all the other centres which shared more than 50% of organs with the rest of the alliance.

2.3.b Balance of exchange with the national pool of organs

In the pre-alliance year, all centres were exporting kidneys to the national pool of organs, the overall balance of exchange of the alliance being +13. This trend continued in the first alliance year with a positive balance of +9. However, in the second year the alliance has imported more kidneys than it has exported (negative balance of -28) to compensate for the positive balance from the previous two years (figure 2.5). More than half of the kidneys imported in the second year went to the largest centre.

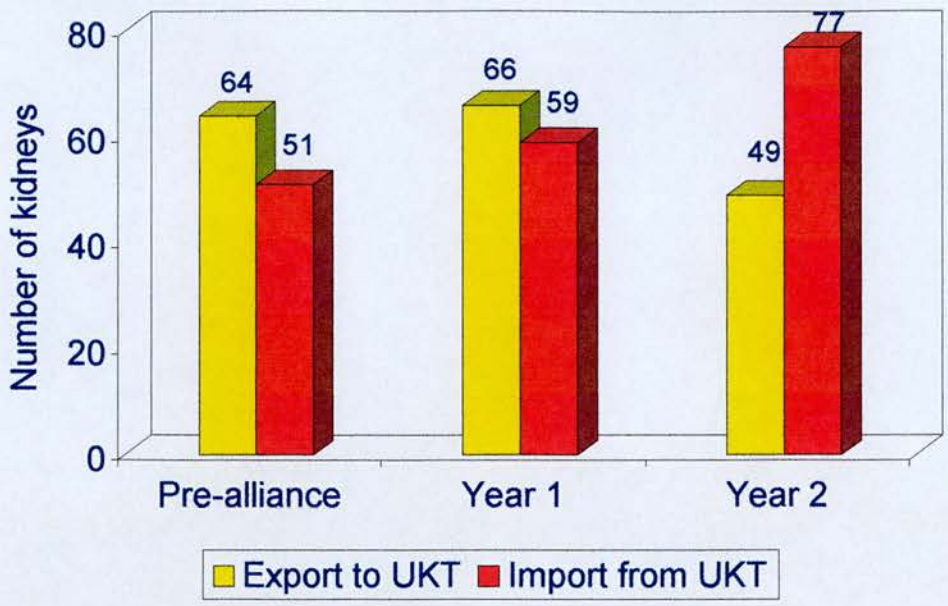


Figure 2.5 Alliance balance of exchange with UKT for each of the three year period

The individual centre balance of exchange with the national pool of organs varied between –2 to +6 in the pre-alliance year and –34 to + 6 in the following two years (figure A.2.a-c, appendix, page 336-337). Before February 2000 the balance was calculated on all exchanges of the previous three years, including kidneys exported for paediatric recipients. However, in February 2000 a new calculation method was introduced counting only kidneys exchanged for adult recipients in the previous two years. Therefore, at the end of the study, on the 1st of September 2000, the individual centre balance of exchange with UKT varied from –45 to +9. There is a significant centre disproportion, the largest centre being a net importer with an increasing negative balance, while all other centres are net exporters (figure 2.6).

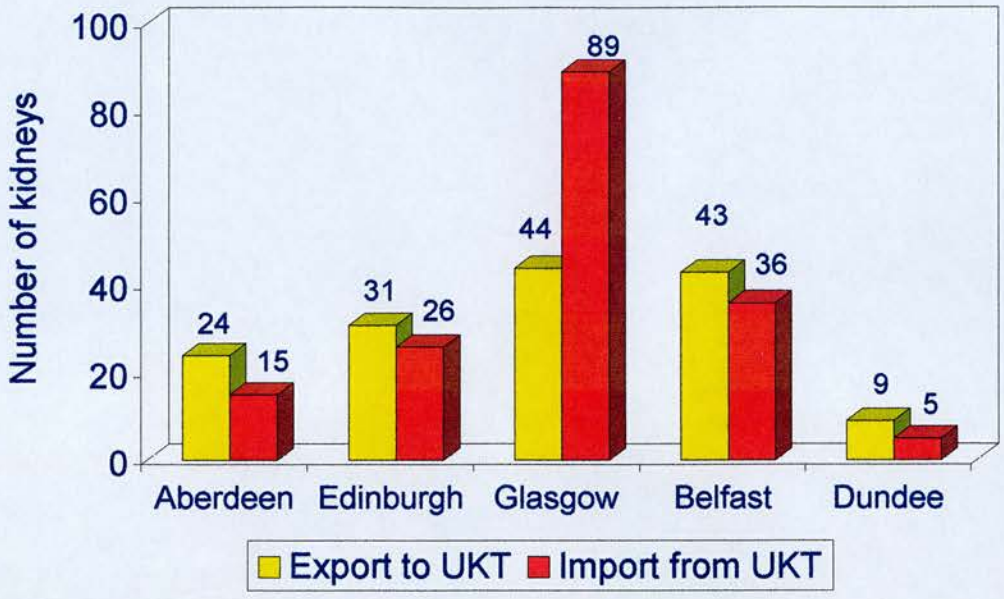


Figure 2.6 Individual centre balance of exchange with UKT at 1st of September 2000.

2.3.c Internal balance of exchange

The internal balance of exchange accounts for the organs exchanged among the participating centres but not for those organs that are transplanted in the retrieving centre. Details for the annual balance of exchange are given in the appendix, table A.9.a-c, page 338. On the 1st of September 2000, due to the change in balance calculation mentioned above, the internal balance of exchange ranged from –18 to +8 (figure 2.7).

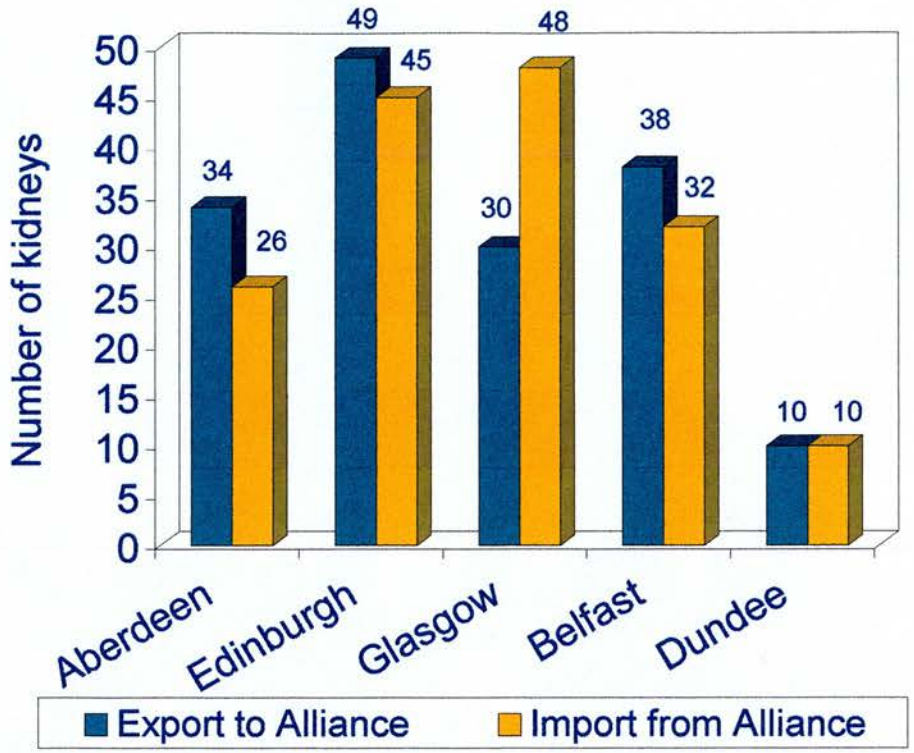


Figure 2.7 Inter-centre balance of exchange on the 1st of September 2000 (end of study).

There is a similar centre disproportion as seen in the external balance of exchange, the largest centre being a constant importer of kidneys from all other centres.

2.3.d Kidney offers

With the introduction of the alliance, there was a 3-fold increase in the number of kidneys offered for transplantation to the participating centres (table 2.4). This translates in 2.4 offers per available kidney in the pre-alliance year, 2.85 in the first

year and 3 in the second year. Details on the offers made to individual centres in the three year period are given in the appendix, table A.10.a-c, page 339).

Year	Number of kidneys offered	Number of kidneys accepted	Number of kidneys accepted and not used (%)	Centre variation (%)
Pre-alliance year	73	49	19 (38)	17-80
Year 1	197	103	34 (33)	6-46
Year 2	222	97	23 (23)	9.5-33

Table 2.4 Number of kidneys offered within the alliance, accepted and accepted and not used (excluding those retained locally)

Over the three year period there was a significant reduction in the proportion of kidneys which were accepted and not used, from 38% in the pre-alliance year to 23% in the second alliance year ($p = 0.031$, χ^2). There is however, a persistent centre variation (17-80% in the pre-alliance year, respectively 9.5-33% in the second year) (table A.10.a-c, appendix, page 339) and various causes may be accountable for it.

A positive crossmatch at the receiving centre remains a significant cause for organ re-allocation throughout the three year period (table 2.5). 63% of the kidneys that were accepted and not used in the pre-alliance year had a positive crossmatch at the recipient centre, these levels being maintained in the subsequent 2 years (67% and

61% respectively). As shown in table A.11.a-c (appendix, page 340), there are significant centre variations throughout the study period.

Centre	Kidneys accepted and not used	Kidneys not accepted due to a positive crossmatch	% Positive crossmatch (centre variation)
Pre-alliance year	19	12	63 (0-100)
Year 1	34	23	67 (33-100)
Year 2	23	14	61 (33-75)

Table 2.5 Kidneys accepted and not transplanted due to positive crossmatching at the receiving centre

2.3.e HLA matching

One of the declared aims of the new allocation scheme was to improve the quality of HLA matching. An analysis of the degree of HLA matching found a significant improvement ($p=0.01$, χ^2) during the first two years of the alliance compared with the previous year (Figure 2.8). Individual centre data are shown in figure A.3.a-e, appendix, page 341-343.

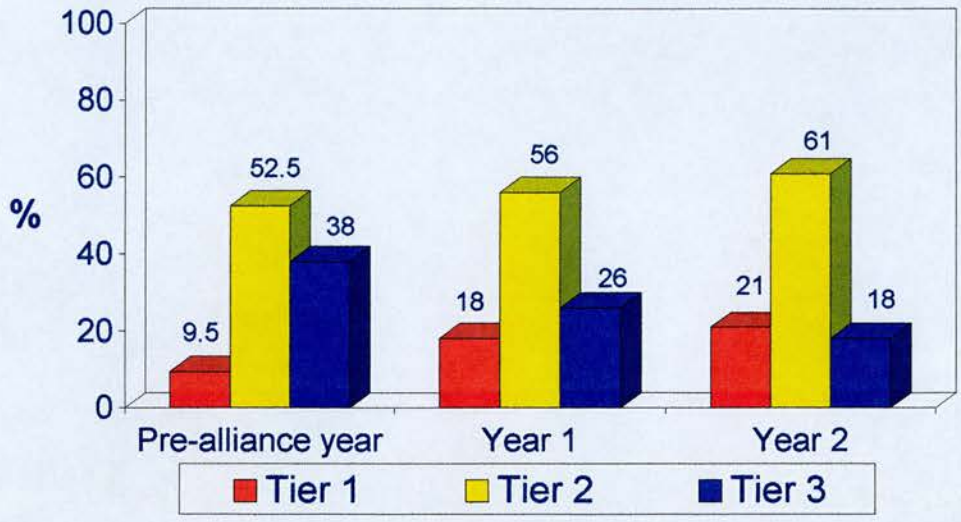


Figure 2.8 % HLA matching for transplants performed within the alliance in each year of activity

By the end of the second alliance year there was an 11.5% increase in the number of fully matched transplants (Tier 1) and an 8.5% increase in the number of favourable ones (Tier 2).

A comparison with the national figures (188) demonstrates that only 64% of the transplants performed in the whole of the UK were very well matched (Tier 1 and Tier 2) in contrast with 79% of the transplants performed in the alliance (table 2.6). The difference is highly statistically significant ($p=0.0001$, χ^2).

Period	No. of transplants	% Tier 1	% Tier 2	% Tier 3	% kidneys transplanted by the retrieving centre
Alliance activity (Sep 1998 – Aug 2000)	352	20	59	21	22
UK activity * (July 1998 – June 2000)	2377	13	51	36	56

Table 2.6 Comparison of Alliance and UK results for the first two years of activity following the introduction of the new allocation scheme (% transplants in each Tier group) (* *UK Transplant Bulletin* 2000; 38: 10-11)

These improvements have been achieved through significant greater organ exchange (33% reduction in locally used organs) ($p=0.0001$, Fisher's 2-tailed t test). On average 78% of kidneys were shipped out of the retrieving centre since the alliance was created, compared with only 44% for the whole of the United Kingdom.

2.3.f Cold ischaemic time

A major concern with the introduction of the new allocation scheme and regional alliances was the effect on the length of the cold ischaemic time (CIT). The three year analysis shows that there is no statistical significant increase (t=0.7018, DF=226, p=0.483, Student t-test) in the length of CIT between the three periods (table 2.7).

Period	Mean (hours)	Std. Dev. (hours)
Pre-alliance year	22.15	9
Year 1	22.28	8
Year 2	22.95	7.2

Table 2.7 Mean CIT for the three periods (unpaired samples Student t-test)

An analysis of the cold ischaemic times according to kidney origin and irrespective of the year of activity (table 2.8) shows no difference (t=1.237, DF=239, p=0.217, Student t-test) between kidneys transplanted by the retrieving centre (L) versus alliance imported organs (A). There is however a significantly longer CIT for UKT imported kidneys (I) compared with both locally used or alliance imported kidneys (t=3.032, DF=251, p=0.002 for I vs. L, respectively t=2.095, DF=248, p=0.037 for I vs. A, Student t-test).

Source	Mean (hours)	Std. Dev. (hours)
Locally used kidneys **(L)**	20.82	8.97
Alliance imported kidneys **(A)**	22.09	6.79
UK imported kidneys **(I)**	24.11	8.29

Table 2.8 Mean CIT for the three sources irrespective of the year of activity (unpaired samples Student t-test)

A further analysis shows that the introduction of the alliance had no effect on the length of CIT, which remained at similar values for both locally used, and alliance shared kidneys (table 2.9).

Period (Source)	Mean (hours)	Std. Dev. (hours)	p value
Pre-alliance year **(L0)**	20.4	9.05	
Year 1 + Year 2 **(L1+L2)**	21.34	8.91	L0 vs (L1+L2), p =0.568
Pre-alliance year **(A0)**	19.57	5.38	
Year 1 + Year 2 **(A1+A2)**	22.83	7	(L1+L2) vs (A1+A2), p=0.267

Table 2.9 Comparisons of mean CIT for locally used and alliance imported kidneys by year of activity. (L= locally transplanted kidneys, A= kidneys imported from other alliance centres, 0= pre-alliance year, 1= first year of the alliance, 2= second year of the alliance) (unpaired samples Student t-test)

2.3.g Graft survival

Despite significant changes in organ allocation and sharing, there has been no decline in the graft survival. From the data reported to UKT, the one year survival rates are comparable for each of the three periods, irrespective of the degree of matching (p=0.1533, Log rank) (table 2.10).

Period	Number transplants in analysis	% survival	95% confidence interval
Pre-alliance year	157	81.5	75.5 - 87.6
Year 1	161	86.8	81.5 - 92.1
Year 2	170	88.4	82.9 - 93.9

Table 2.10 One year graft survival for the transplants performed in each year (p=0.1533, Log rank test)

When the survival analysis incorporated the number of mismatches as well as the transplant era, the one year graft survival for fully matched transplants improved from 86.7% in the pre-alliance year to 88.9% in the post-alliance era. For the other levels of matching the improvement was from 79.5% to 85.4% for tier 2 and from 83% to 93.8% for tier 3 respectively (table A.12.a-c, appendix, page 344). These changes did not reach statistical significance.

2.3.h Waiting list composition

Between 1st of September 1998 (beginning of the alliance) and 1st of September 2000 (end of the two year period) there has been a reduction in the proportion of long-waiting patients (> 5 years) from 11.2% to 10.4% and in the proportion of highly sensitised (PRA> 85%) patients from 9% to 7.3%. Similarly the proportion of re-transplanted patients decreased from 27.1% to 25.6%.

2.4 DISCUSSION

The widening gap between the supply and the demand of cadaveric kidneys, has highlighted the controversial issue of allocation of donor organs to recipients (189;190). Introduced nearly two decades ago (109), allocation schemes are constantly reviewed in an attempt to achieve an optimal balance between the best use of a scarce resource and equity of access (110-112;187;188). Extensive work by Terasaki et. al. in Los Angeles, proving the benefit of better HLA matching (91), forms the theoretical basis of the modern allocation systems. Recent data from the USA (110;111) and Europe (187) have shown that the new allocation schemes based on HLA matching have improved the allocation of donor organs.

In July 1998, the UK transplant community adopted a new allocation scheme for adult kidneys (17) which was described in chapter 1. This acknowledges the degree of HLA matching as the main factor determining the fate of the kidney. The length of waiting time, the degree of sensitisation and geographical factors are taken into account and points are allocated for each criterion. The new scheme gives priority to local patients, and therefore the concept of regional alliances experienced a new revival. However, there are concerns about the practicality of larger alliances, in particular about the future of the small participant transplant programmes and of those centres that opted to remain outside alliances.

The retrieval activity in Scotland and Northern Ireland was not influenced by the introduction of the new alliance and the decrease noted in the second alliance year

was consistent with the national reduction in donation rates. These levels of retrieval are still low compared with other countries, but above the UK average for the same periods (30). It is worth mentioning that during the study period, the rate of irremediable organ damage during retrieval was only 2%, which is an improvement from that which was previously reported in UK (191). The reduction in retrieving activity is set against an increase by 11% in the number of transplants performed since the alliance was introduced, this being largely due to an average 30% increase in the number of kidneys imported from outwith the alliance.

There has been a significant improvement in the degree of HLA matching, by the end of the second year nearly 80% of the transplants being either fully or favourable matched. It could be argued that some of the improvement in matching has resulted from the introduction of the new allocation scheme for the UK two months before the Scotland-Northern Ireland alliance was created. However, as shown by these data, there is a 15% better matching in the alliance compared with the national figures (188). In addition, in the second year of the alliance, when no more changes were made to the national allocation system, there was a further 8% improvement in matching in the alliance compared with only 2% for the UK activity. Furthermore, the higher degree of matching was achieved through an increased organ exchange. In the pre-alliance year all the exchanges amongst centres were done solely through the national pool, with 45% of the kidneys being retained by the retrieving centre. Since the alliance was founded, the exchange with the national organ pool has remained at similar levels, but this additional level of sharing has led to 28% more kidneys being exchanged regionally, between the four participating centres. This contributed to

significantly higher levels of kidney sharing in the alliance when compared with the national activity. By the end of alliance's second year, for each accepted kidney, two more offers were made indicating the scale of the organ exchange process. And finally, comparing the structure of the waiting list at the beginning of the alliance and at the end of the two year period, there was a reduction in the proportion of the long waiting patients, highly sensitised patients and re-transplants on the waiting list. These points suggest that there is indeed an added benefit of a regional waiting list alliance and one can safely say that the goal of increased exchange of favourable matched kidneys between participating centres has been accomplished.

The main worry expressed by the critics of these types of schemes (188;192), was the deleterious effect of a longer CIT due to an increased organ exchange and shipping which would diminish the benefit of a better HLA match. Although obtaining an accurate recorded CIT may prove sometimes difficult, these data from the National Transplant Database demonstrate that there is no difference between kidneys imported from the alliance and those transplanted by the retrieving centre or between the pre- and post-alliance era. The cold ischaemic times may vary significantly from centre to centre, but these results suggest that perhaps other local elements such as access to theatre rather than an increased organ sharing should be investigated as causal factor. Similarly, there is no detrimental effect on the graft survival. From the data reported to the national transplant organisation, the one year graft survivals are similar if not better for all levels of matching since the alliance was created.

A serious concern was the effect of regional alliances on the small and medium size participating transplant programmes. Previous studies reported that smaller centres tend to become relative exporters due to the size of their recipient pool (193), this effect being counterbalanced by a higher rate of unfavourable HLA matched transplants (117). A similar imbalance, was noticed in the international exchanges between different sized programmes at the beginning of the new Eurotransplant allocation scheme (187). As recently reported at the European society for Organ Transplantation meeting in Lisbon (194), this imbalance still persists even five years after the implementation of the scheme. It has been argued that a centre with a larger waiting list has a mathematically higher probability of attracting more donor kidneys. To counterbalance the effect of waiting list size, most allocation systems include a balance of exchange criterion. As Scotland-Northern Ireland alliance includes a large centre and four other medium or small sized centres, a similar analysis was possible. At the end of the three year study period, all small and medium size centres were net exporters of kidneys to the national pool in order to compensate for the increasing negative exchange balance of the large centre. The internal balance of exchange had a similar profile, with the largest centre importing organs from the rest of the alliance. Despite the fact that the centre balance of exchange is one of the scoring system criteria, two years since the introduction of the new allocation scheme, there is a persistent centre disproportion which will need to be addressed properly and not just by a balance rollover.

A recent report from UKT (195) highlighted the fact that one in four offers are accepted but subsequently have to be reallocated, in 61% due to a positive

crossmatch at the receiving centre. Similar levels were observed within the Scotland-Northern Ireland Alliance, and there has been no improvement since the introduction of the new sharing scheme. It is therefore important that uniformity between the authorized laboratories should be achieved in order to minimise the unnecessary shipping or loss of kidneys. Some have even suggested regional centralization (196) as the way forward.

2.5 CONCLUSION

In summary, a series of questions were raised at the beginning of the study:

1. Is there an improvement in the level of HLA matching in a wider alliance?
2. Is there a longer cold ischaemic time with increased organ sharing?
3. What impact has the alliance on the activity of a large centre?
4. What impact has the alliance on the activity of a small centre?

All these questions were answered by this analysis. Despite a status quo of the retrieval activity, following the introduction of the Scotland-Northern Ireland alliance, the number of kidney transplants has increased, with a substantial improvement in the proportion of favourable matched kidneys and a higher exchange rate.

Experience within the Scotland-Northern Ireland alliance, applying the UK allocation criteria, shows a clear benefit of improved HLA matching without any detrimental effect on the length of CIT or graft survival.

There is however, a persistent disproportion in kidney distribution amongst the participating programmes, the largest centre receiving a significant proportion of all organs shared within the alliance. Although this will require correction, the ways to do it may not be as easy as it seems.

This study has shown that changes at this stage of the clinical pathway to transplantation have resulted in an improved matching which could create the basis of better long-term results. Nevertheless, one question remains and that is whether or not there is equity of access to the transplant waiting list and renal transplantation.

CHAPTER 3

EQUITY OF ACCESS TO THE RENAL TRANSPLANT WAITING LIST AND RENAL TRANSPLANTATION IN SCOTLAND

3.1 INTRODUCTION

The number of patients starting renal replacement therapy in Scotland has risen sharply in the last decade (figure 3.1).

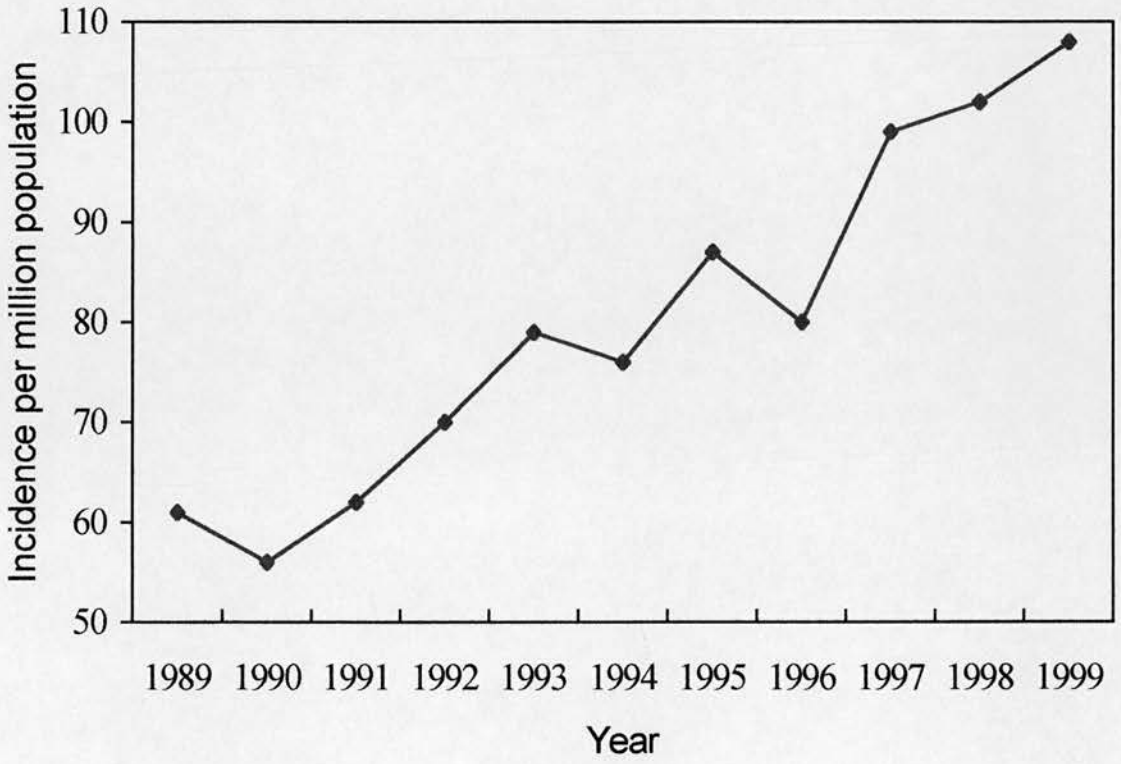


Figure 3.1 Annual incidence per million population of new patients starting RRT 1989-1999 (Source: Scottish Renal Registry)

Kidney transplantation has been shown to be the most successful, economical and cost-effective (18;21) form of treatment that improves the quality of life (24;25;197)

and survival for these patients (19;21;152) and therefore should represent the gold standard when considering treatment options for these patients.

However, not all patients receiving dialysis are suitable for transplantation (198). Furthermore, there is evidence from United Kingdom (199;200) and elsewhere (131;155) that selection criteria vary widely. Because of an increasing demand, yet a diminishing supply of donor organs (figure 3.2), there is a rising pressure on the transplant community to devise appropriate selection criteria to optimise the use of this scarce resource.

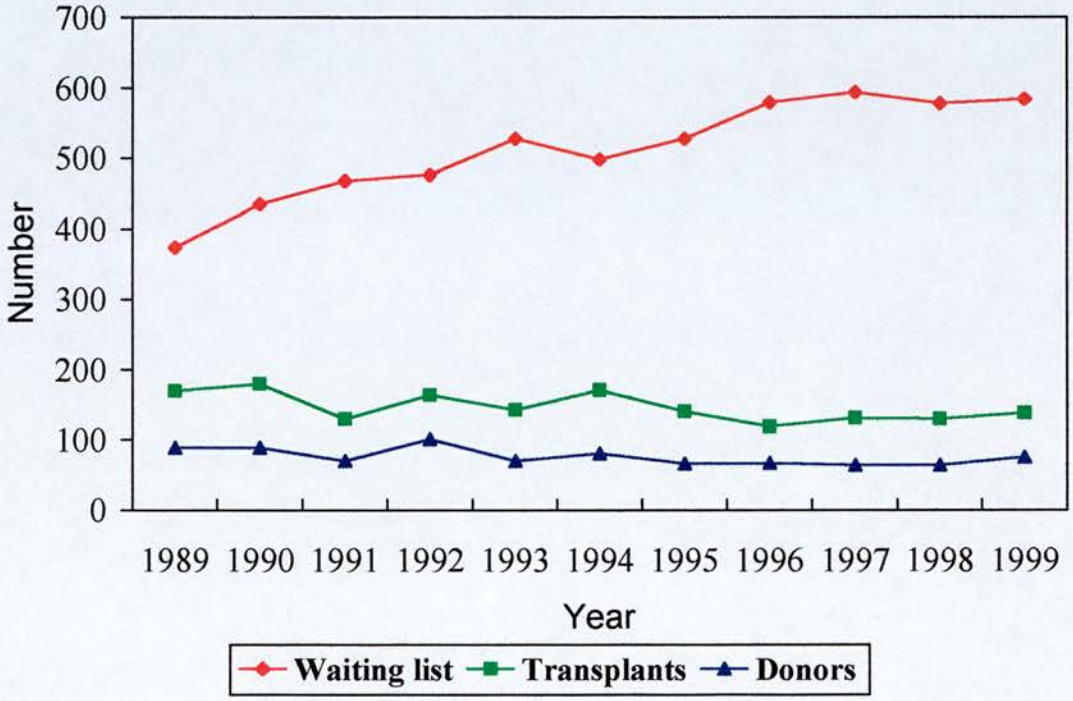


Figure 3.2 Number of patients on the waiting list, number of donors and number of kidney transplants in Scotland 1989-1999 (*Source: United Kingdom Transplant*)

Nevertheless, as highlighted in the "Renal Association treatment of adult patients with renal failure standards and audit measures" (201) it is equally important to ensure that there is equity of access to transplantation irrespective of age, gender, race, district of residence and social welfare. Since the inception of the National Health Service in Britain there have been concerns about equity of access to health care (202;203) and priorities in access to renal transplantation have also come under scrutiny (204). A sequence of potential barriers along the clinical pathway to transplantation has been previously documented (123) and there is a growing body of evidence, coming mainly from the USA demonstrating that transplantation rates vary significantly across different age (143), gender (125;205) and race (132;206;207) groups. The likelihood of a patient being listed for transplantation and transplanted is significantly associated with the health status as well as socio-economic and geographic factors (130;208;209).

In order to investigate whether inequities in access to the renal transplant waiting list and renal transplantation are present in Scotland, we performed a longitudinal analysis on all adult patients starting dialysis between 1st of January 1989 and 31st of December 1999. This study, one of the first of its type in UK, investigates the relationship between socio-economic and geographic factors and access to the renal transplant waiting list and renal transplantation, following a patient from the first renal replacement therapy through to listing for transplantation and beyond.

3.2 METHODS

3.2.a Patient population

The study population consisted of all adult patients (age >18 years old) who started ESRD therapy in Scotland between 1st of January 1989 and 31st of December 1999. Patients were followed to listing and then on to first transplant, death or study end (31st of December 2000). Patients were identified using the Scottish Renal Registry (SRR) and United Kingdom Transplant (UKT) databases.

The Scottish Renal Registry is a comprehensive database for all patients receiving replacement therapy in all renal units in Scotland. It provides information regarding the date of birth, gender, primary disease causing ESRD, date and type of first dialysis, treatment changes, dialysis and transplant centre and patient survival. Furthermore, a postcode of residence for each patient is held in the database. This allows the determination of a map reference - used to calculate the distance between the patient's home and the transplant centre - and also, the measurement of social deprivation by means of the Carstairs score. This score is a complex calculation, which is derived from the census and is based on a combination of four variables (male unemployment, car ownership, social class and overcrowding) (210) (table A.13, appendix, page 345).

The deprivation scores for each postcode sector (211) range from –8.48 (affluent) to +12.82 (deprived) and are classified into seven categories from 1 – which is the least deprived to 7 – which is the most deprived (table 3.1).

Score	Category	Population (%)
< -5	1 most affluent	6
-5 < -3	2	14
-3 < -1	3	22
-1 < +1	4	25
+1 < +3	5	15
+3 < +6	6	11
+6 < +13	7 most deprived	7

Table 3.1 Deprivation scores grouped into categories and proportion of Scottish general population in each category

The United Kingdom Transplant database records the transplant waiting list and transplant activity in UK and provides demographic data, date of listing for an active transplant waiting list, the length of time on active waiting list and periods of suspensions, the date of a transplant if one is performed as well as follow-up data including patient and graft survival.

Because the two databases did not contain unique identifying variables, a combination of birthdate and gender were used to match the patients, after obtaining ethical approval from the local ethical committee and preserving patients' anonymity in accordance with the relevant legislation.

3.2.b Exclusions from the study

In total 408 cases (9%) were excluded from the analysis. They included patients who received a renal transplant as their first mode of end stage renal failure therapy (44),

patients who were registered for transplantation prior to commencing renal replacement therapy (123), patients registered in more than one centre during the analysis period and patients with missing data. Because some patients were temporarily removed from the waiting list due to medical illness or other reasons, all periods of suspension were excluded and only the time on the active waiting list was used in the analysis of access to transplantation.

3.2.c Outcome

The clinical outcomes were listing for transplantation and transplantation. Patients dying before either of these events were censored at the time of death. Similarly, patients permanently removed from the waiting list were censored at date of removal while those patients still waiting to be listed (for access to the waiting list) or on the active waiting list (for access to transplantation) at 31st of December 2000 were censored at that time.

3.2.d Statistical analyses

The factors associated with the likelihood of listing in the dialysis population and those associated with the likelihood of transplantation in the waiting list population were investigated using both univariate and multivariate Cox proportional hazards regression analysis. On the basis of log cumulative hazards plots there was no

evidence of non-proportionality across the various factors used in this analysis. The results are presented in terms of relative risks between groups of patients, compared with that of a reference group. A relative risk of greater or less than 1.0 indicates respectively, a higher or a lower risk than in the reference group. For each relative risk, 95% confidence intervals (CI) were calculated. Kaplan Meier curves were used to determine the median time to listing and transplantation and the p values were derived from a univariate log rank test. A 5% level of significance was used throughout the analyses, which were carried out using SPSS software, version 9.0.

a. Access to the transplant waiting list

For each variable two indicators of access were analysed: i.) the proportion of patients being listed within three years of starting renal replacement therapy and ii.) the length of time spent on dialysis before listing. In the absence of a variable in the Renal Registry which can identify patients who will never be suitable for listing and transplantation, the median time of access to the waiting list was calculated using an "intention to treat" approach whereby all patients starting RRT were considered suitable for listing. This method, although statistically correct, does not give a true indicator of how long it actually takes for someone considered suitable for transplantation to be listed. Therefore, a separate analysis, taking into account only those patients listed within the study period, was performed as an indicator of current clinical practice.

The variables considered were:

- patient's age when starting replacement therapy
- gender
- social deprivation
- distance from patient's home to the transplant centre
- primary renal disease
- type of first dialysis and year of 1st RRT
- centre where 1st RRT was performed
- centre of listing for transplantation

The primary renal disease was coded using the EDTA-ERA code list and grouped into five categories (32) to simplify the analysis: glomerulonephritis, interstitial nephritis, diabetic nephropathy, multi-system disorders and other/unknown diagnosis. Age was divided into 5 groups according to the ones used by the UK Transplant: 18 to 34 years, 35 to 49 years, 50 to 59 years, 60 to 65 years and 65 years and older. The linear distance from patient's home to the transplant centre was analysed as a continuous variable as well as a categorical one (less than 50 km, 50 to 100 km and more than 100 km). Each renal unit and listing/transplant centre was randomly numbered. To investigate the centre effect two separate models were built. The first one included socio-demographic data and whether or not patients started dialysis in a unit situated in the same hospital as a transplant centre. The second model contained the same socio-demographic data and grouped the patients according to the four transplant centres where they were referred for listing.

b. Access to transplantation

The indicators of access analysed were:

i. the proportion of patients transplanted within three years of listing and

ii. the length of time spent on the active waiting list.

The median time of access to transplantation from listing was calculated excluding the periods of suspensions, as patients were not exposed to the risk of transplantation during these intervals. The same variables as before were included, plus the time from 1st RRT to listing. Age at listing rather than age at the beginning of RRT was considered.

3.3 RESULTS

4532 adult patients started replacement therapy in Scotland between 1st of January 1989 and 31st of December 1999. 1736 (38.38%) of these patients were listed for transplantation and 1095 (24.20%) received a kidney transplant by the end of the follow-up period. The mean age at the onset of RRT was 57.73±16.03 years (mean±SD), while the mean ages at listing and transplantation were 46.60±14.14 years (mean±SD) and 44.30±13.52 years (mean±SD) respectively. The median time of access to the waiting list was 2.84 years while the median time from listing to transplantation was 1.74 years (95%CI: 1.55-1.92).

3.3.I Access to the waiting list

Univariate analysis

Table 3.1 shows the distribution of gender, age, deprivation category, primary renal disease and the type of first RRT modality at the onset of RRT and the proportion of patients from each group listed for transplantation within three years of 1st RRT.

	% of RRT population in this group	% of group on WL at 3 years	Relative rate of listing Cox regression (C.I.)	p value
Gender				0.0075
Male (ref. group)	58.3	38.3		
Female	41.7	33.7	0.87 (0.78-0.96)	
Age groups				<0.0001
18-34 (ref. group)	10.8	82.9	1	
35-49	16.1	69.4	0.76 (0.66-0.87)	
50-59	17.5	55.7	0.46 (0.30-0.53)	
60-64	13.7	26.3	0.21 (0.17-0.25)	
>65	41.8	8.5	0.07 (0.59-0.87)	
Deprivation category				0.0019
1 (ref. group)	4.9	36.9	1	
2	12.6	35.5	0.99 (0.76-1.30)	
3	21.9	41.2	1.07 (0.84-1.38)	
4	25.2	37.4	0.95 (0.74-1.22)	
5	15.0	33.9	0.84 (0.65-1.09)	
6	12.9	35.7	0.87 (0.67-1.14)	
7	7.5	26.3	0.67 (0.49-0.92)	
Primary renal disease				<0.0001
Primary GN (ref. group)	16.4	57.9	1	
Interstitial nephritis	20.8	50.9	0.80 (0.70-0.92)	
Multisystem disease	24.0	22.7	0.37 (0.31-0.43)	
Diabetes	16.3	33.5	0.53 (0.45-0.62)	
Other/unknown	22.5	24.0	0.39 (0.33-0.46)	
Type of first dialysis				<0.0001
Haemodialysis	70.2	30.9	1	
Peritoneal dialysis	29.8	49.7	1.49 (1.34-1.65)	

Table 3.1 Socio-demographic and end-stage renal disease distribution of the RRT population, proportion on the waiting list (WL) at three years after starting RRT and relative rates of listing for subgroups (Univariate Cox regression analysis)

Gender

There is an imbalance in access to the waiting list based on gender, females being less likely to be listed for transplantation compared with males, as shown in table 3.1. Moreover, the median time of access for males (2.11 years) is significantly shorter (p= 0.0074, Log rank test) than the median time of access for females (5.03 years) (figure 3.3).

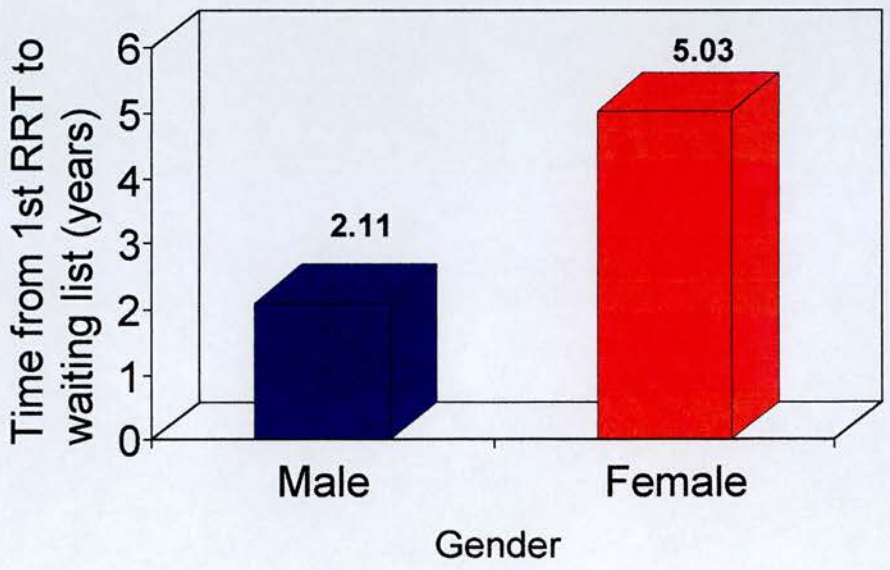


Figure 3.3 Median time of access to the waiting list by gender

Age at 1st RRT

As expected, there is a trend towards the older patients requiring replacement therapy. 41.8% of all adults starting RRT were over 65 years old and only 11% were younger than 35 years old (table 3.1). However, the proportions listed from each age group at three years show a completely opposite trend, 83% in the youngest age group being listed compared with only 8.55% in the eldest one. In addition, the older the patient, the more time spent on dialysis prior to listing ($p<0.0001$, Log rank test). Less than 50% of the patients in age groups 60-64 and >65 were listed within 9 and 11 years respectively (figure 3.4).

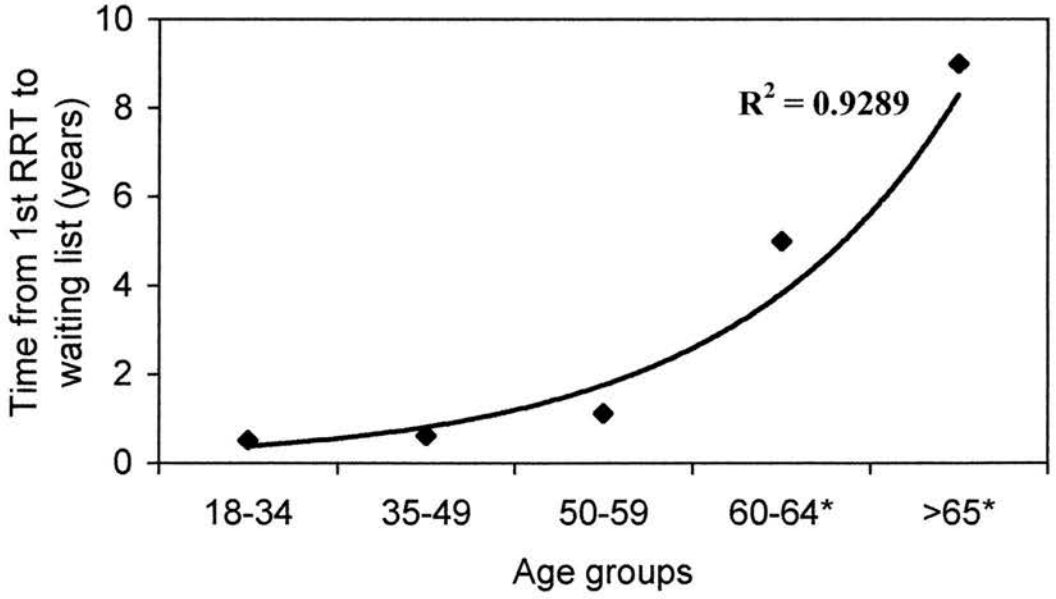


Figure 3.4 Median time of access to the waiting list by age groups (Analysis limited at this time point as less than 50% of the patients were listed)

Deprivation category

The deprivation category profile of the RRT population is statistically identical with that of the Scottish general population (figure 3.5). Three years after starting renal replacement therapy, the proportion of patients from each deprivation category admitted onto the waiting list is significantly different (table 3.1) (p=0.0019, Cox regression analysis).

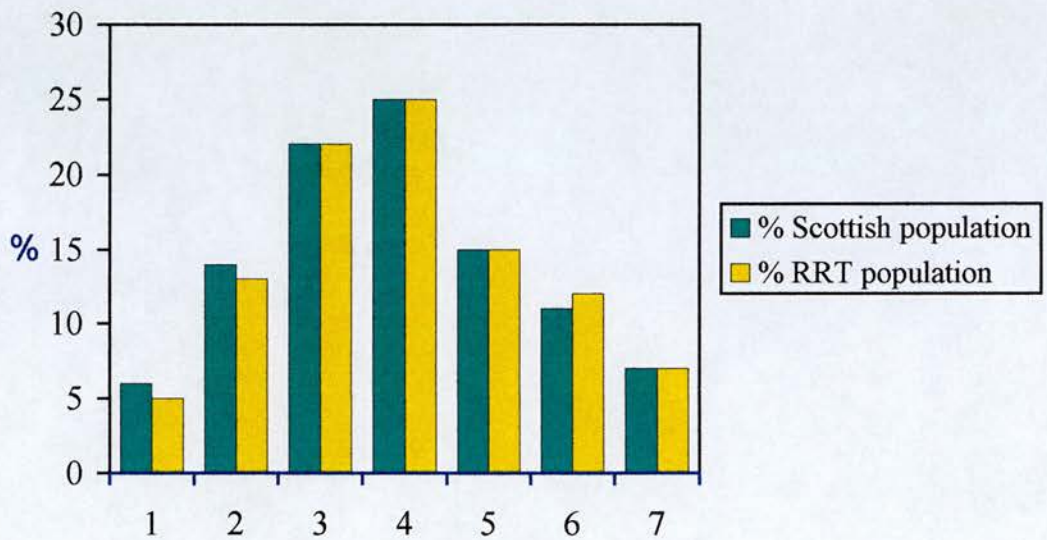


Figure 3.5 Social deprivation distribution for the RRT population compared with Scottish general population (Carstairs groups, 1=least deprived, 7 = most deprived)

There is a significant disparity in the length of time spent on replacement therapy prior to listing, patients in group 7 (the most deprived) being the longest waiting patients (figure 3.6).

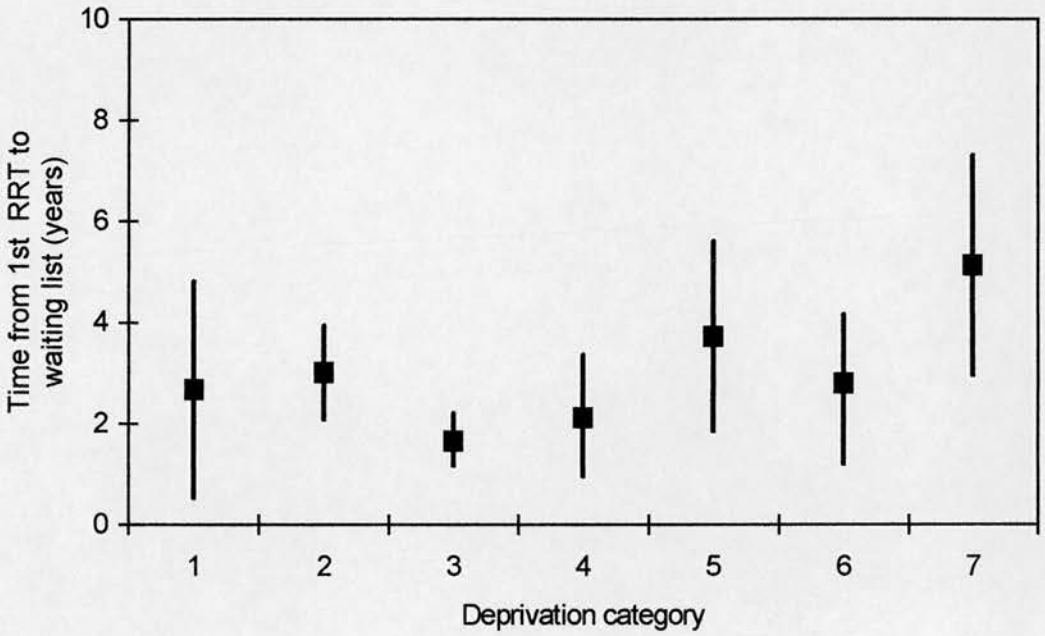


Figure 3.6 Median time of access to the waiting list by deprivation category

Primary renal disease

The proportions of patients listed within 3 years of 1st RRT are illustrated in table 3.1. Multi-system disease was the recorded cause of renal disease in nearly a quarter of the RRT population, but these patients had the lowest chance of listing ($p<0.0001$, Cox regression analysis). Diabetes caused renal failure in 16.3% of the patients but only one in three diabetics was listed within three years. There are huge differences

in the length of time spent on dialysis prior to admission onto the waiting list (figure 3.7). Patients with diabetes as primary renal disease wait the longest time amongst patients with known causes of renal failure, more than 50% of those starting RRT not being listed within 10 years ($p<0.0001$, Log rank test).

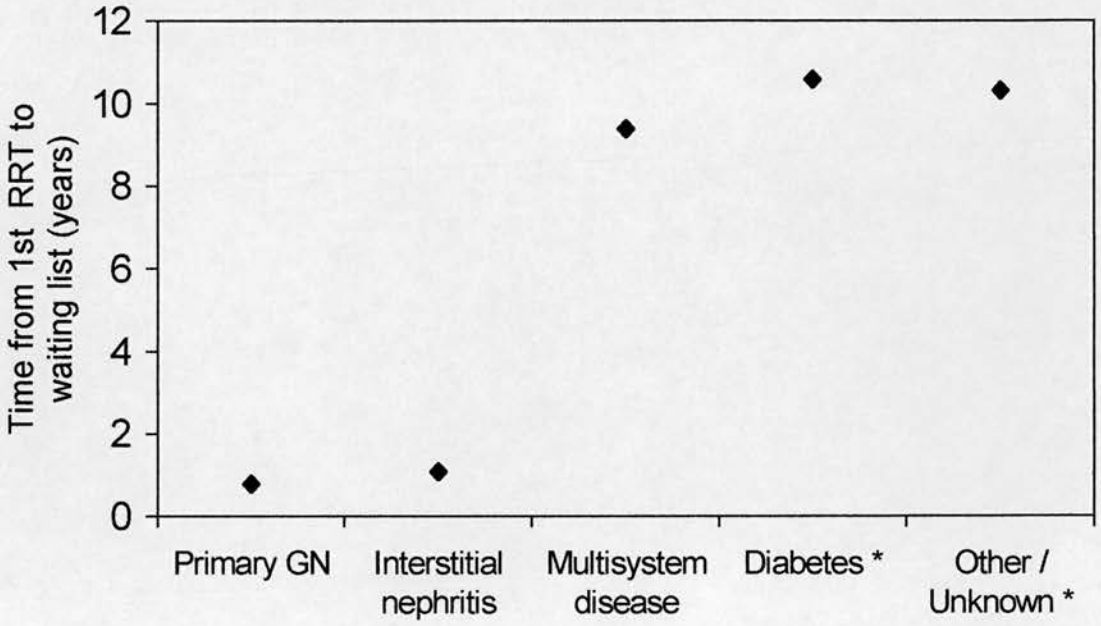


Figure 3.7 Median time of access to the waiting list by primary renal disease

Type of first RRT

The type of first renal replacement therapy is chosen according to the patient's general status, primary disease, tolerance and ease of use. There are a significant number of patients who will switch between treatment modalities and therefore the influence of this variable is difficult to quantify. 70% of the patients in this cohort

started on haemodialysis while the remaining patients started on peritoneal dialysis. Only 30% of haemodialysis patients were listed and did so after a significantly longer time (median time 4.5 years) on replacement therapy compared with peritoneal dialysis treated patients (median time 1.23 years) ($p<0.0001$, Log rank test).

Renal unit

In Scotland, there are 11 adult renal units, which are allocated to one of four transplant centres (at that time) based on geographical criteria. Four of the renal units are situated in the same hospital as a transplant centre. There are significant differences in the proportion of patients being listed within three years of starting RRT (table 3.2) as well as in the length of time spent on dialysis pre-listing according to the renal unit where the patients starts replacement therapy.

Furthermore, patients treated in the four renal units situated in the same hospital as a transplant centre (57% of the cohort) are more likely to be listed ($p<0.0001$, Cox regression) and wait significantly shorter compared with the remaining patients (1.94 years versus 4.4 years) (table 3.3).

	% of RRT population in this group	% of group on WL at 3 years	Relative rate of listing Cox regression (C.I.)	p value
Renal unit (1st RRT)				<0.0001
1	9.3	52.2	1	
2	10.8	41.7	0.73 (0.60-0.89)	
3	16.3	37.0	0.47 (0.39-0.57)	
4	20.8	31.9	0.42 (0.35-0.50)	
5	14.2	36.2	0.46 (0.38-0.56)	
6	5.5	27.6	0.34 (0.26-0.45)	
7	3.5	30.1	0.44 (0.32-0.61)	
8	3.0	21.3	0.27 (0.18-0.41)	
9	5.4	34.2	0.42 (0.32-0.55)	
10	3.7	41.7	0.62 (0.47-0.82)	
11	7.7	34.9	0.46 (0.36-0.57)	
Renal unit in same hospital with Tx centre				<0.0001
Yes	57.1	38.5	1	
No	42.8	33.5	0.79 (0.71-0.87)	
Listing transplant centre				<0.0001
Centre 1	12.5	49.4	1	
Centre 2	9.7	41.2	0.83 (0.68-1.01)	
Centre 3	19.7	34.7	0.51 (0.43-0.61)	
Centre 4	58.0	33.3	0.50 (0.43-0.57)	
Distance to listing centre (as a linear variable) (per km)			1.0018 (1.0007-1.0029)	0.0014
Distance to listing centre				0.0287
<50 km	83.7	35.7	1	
50 – 100 km	7.2	41.9	1.19 (0.99-1.42)	
>100 km	7.2	39.0	1.22 (1.01-1.47)	

Table 3.2 Geographic distribution of the RRT population, proportion on the waiting list (WL) at three years after starting RRT and relative rates of listing for subgroups (Univariate Cox regression analysis)

When the units were grouped by the listing centre to which they are geographically allocated, there was a bimodal distribution, with two of the centres listing patients within a year, while the median waiting time for the remaining two was longer than 3.7 years (table 3.3).

Distance to listing centre

When the linear distance between the patient's home and the listing centre was calculated (table 3.2), it was found to be a significant predictive factor of access to the waiting list ($p=0.0014$, Cox regression) (distance as a linear variable analysis). When distance was analysed as a categorical variable (<50 km, 50-100 km, >100 km), the difference between the proportions of patients listed from each group was significant and furthermore, there was a significant trend towards shorter waiting time, the further away from the unit the patient lived ($p=0.0283$, Log rank test) (table 3.3).

When an analysis was carried out limited to those patients listed during the study period, the results shown in table 3.3 indicate that all factors, except gender, maintain a significant influence on the median time of access to the waiting list.

Factors in analysis	Access to the waiting list			
	All patients[+]		Listed patients[++]	
	Median time (years)	P value (Log rank)	Median time (months)	P value
Gender		0.0074		0.715*
Male	2.14		5.95	
Female	5.03		5.95	
Age groups		<0.0001		<0.0001**
18-34	0.52		5.28	
35-49	0.59		5.16	
50-59	1.16		7.08	
60-64	>9.33[†]		7.56	
>65	>11.01[†]		7.08	
Deprivation category		0.0018		<0.0001**
1	2.94		5.04	
2	3.13		4.80	
3	1.69		5.76	
4	2.4		6.00	
5	4.38		6.60	
6	2.80		6.72	
7	5.13		6.72	
Primary renal disease		<0.0001		<0.0001**
Primary GN	0.79		5.52	
Interstitial nephritis	1.09		5.88	
Multisystem disease	9.39		8.04	
Diabetes	>10.59[†]		5.40	
Other/unknown	>10.32[†]		6.84	
Type of first RRT		<0.0001		0.001*
HD	4.5		6.36	
PD	1.23		5.28	
Renal unit in the same hospital with a Tx centre		<0.0001		<0.0001*
Yes	1.94		5.16	
No	4.64		6.72	
Transplant centre		<0.0001		<0.0001**
Centre 1	0.88		3.84	
Centre 2	0.98		4.68	
Centre 3	3.73		6.84	
Centre 4	5.03		6.60	
Distance to listing centre		0.0283		0.04**
<50 km	3.29		6.00	
50 – 100 km	1.99		5.04	
>100 km	1.47		6.00	

Table 3.3 Median time of access to the waiting list

[[+] "intention to treat analysis"; [++] patients listed during the study period] (*- Mann-Whitney U test; **- Kruskal-Wallis test; [†] - analysis limited at this time point as less than 50% of the patients listed)

Multivariate analysis

A proportional hazards model, which included the year of first RRT in addition to all of the above covariates, was built. Table 3.4 shows the relative rates (RR) of access to the renal transplant waiting list for the various covariates and their corresponding p values. The listing rates in the reference groups are arbitrarily assigned a value of 1.0 and the comparison group's RR are expressed relative to the reference group.

Women have a 19% lower listing rate than men (RR=0.81; $p<0.0001$), other covariates equal. Relative to patients 18 to 34 years of age, listing rates decline the older the patient. Patients aged 60 to 64 years old have a 79% lower listing rate compared with the reference group (RR=0.21, $p<0.0001$), while those over 65 years old have very little chances of listing, their rate being 93% lower than the youngest group (RR=0.07, $p<0.0001$).

Social deprivation remains a significant predictor of access to the waiting list. All other covariates equal, the relative rate of listing decreases with increased deprivation, when compared with the reference group (group 1 = least deprived).

Patients with diabetes causing ESRD have the lowest rate of listing (RR=0.50, $p<0.0001$) when compared with those with glomerulonephritis and they are followed by patients with multisystem disease (RR=0.54, $p<0.0001$).

Peritoneal dialysis as the first RRT modality has a positive effect on the access to the waiting list, these patients having a 46% better chance of listing compared with those haemodialysed (RR=1.46, 95%CI: 1.32 – 1.64).

	The relative risk (95% CI) of access to the waiting list	p value Cox regression
Gender		
Male (reference group)	1	
Female	0.81 (0.73 – 0.90)	<0.0001
Age groups		
18-34 (reference group)	1	
35-49	0.75 (0.65 – 0.86)	<0.0001
50-59	0.44 (0.38 – 0.51)	<0.0001
60-64	0.21 (0.17 – 0.25)	<0.0001
>65	0.07 (0.06 – 0.08)	<0.0001
Deprivation category		
1 (reference group)	1	
2	0.69 (0.53 - 0.91)	0.008
3	0.72 (0.56 – 0.93)	0.011
4	0.66 (0.51 – 0.84)	0.001
5	0.57 (0.44 – 0.75)	<0.0001
6	0.62 (0.47 – 0.81)	0.001
7	0.54 (0.39 – 0.74)	<0.0001
Primary renal disease		
Primary GN (ref. group)	1	
Interstitial nephritis	0.78 (0.68 – 0.90)	0.001
Multisystem disease	0.54 (0.45 – 0.64)	<0.0001
Diabetes	0.50 (0.42 – 0.58)	<0.0001
Other/unknown	0.60 (0.51 – 0.72)	<0.0001
Type first RRT *PD vs. HD*	1.468 (1.32 – 1.64)	<0.0001
Renal unit adjacent to a Tx centre *		
Yes (reference group)	1	
No	0.72 (0.65 – 0.80)	<0.0001
Listing transplant centre**		
Centre 1 (reference group)	1	
Centre 2	0.88 (0.71 – 1.09)	0.244
Centre 3	0.44 (0.36 – 0.53)	<0.0001
Centre 4	0.38 (0.32 – 0.45)	<0.0001
Distance to listing centre		
0-50 km	1	
50-100 km	1.12 (0.92 – 1.40)	0.255
> 100 km	0.69 (0.55 – 0.85)	0.001
Year of 1st RRT, *per year*	0.95 (0.93 – 0.97)	<0.0001

Table 3.4 Relative risks of access to the transplant waiting list (Cox proportional hazards model) (*-model including renal unit in same hospital with Tx centre, **-model including transplant centre)

The rate of listing for transplantation is 28% lower (RR=0.72, p<0.0001) for patients who start RRT in a renal centre which is not in the same hospital as a transplant unit. The distance from patient's home to listing centre remains a predictive variable of access to the waiting list (p=0.001) even in the multivariate analysis, while the centre effect is persistent, with patients referred for transplantation to centres 1 and 2 being more likely to be listed compared with patients in centres 3 and 4, who have almost 60% lower listing rates. The year of onset of RRT is a significant factor and there is a 5% reduction in listing rates with each year closer to the end of the follow-up period (RR=0.95, p<0.0001).

3.3.II Access to transplantation

Univariate analysis

Once a patient is listed, an analysis of the proportion of patients transplanted within three years of continuous listing (only time spent on the active waiting list considered) (table 3.5) and the median time to transplantation was performed (figure 3.8).

Age remains a significant independent factor governing access to transplantation, the elderly the patient, the lower the proportion on the waiting list and the longer the waiting time (p<0.0001, Cox regression).

Also, there are significant differences in access to transplantation based on the primary renal disease, patients with multisystem disease waiting longest prior to transplantation ($p=0.001$, Cox regression).

The time spent on dialysis pre-listing has a significant impact ($p=0.0062$, Cox regression) on access to transplantation, the chance of transplantation decreasing by 15% for each additional year spent on dialysis.

There are significant centre variations ($p<0.0001$, Cox regression), but they are mainly due to one centre (centre 2), where patients wait significantly longer (3.95 years) and have a reduced chance of transplantation once listed, compared with the remaining three centres (table 3.5).

	% of WL population in this group	% of group Tx at three years	RR Cox regression (C.I.)	p value
Gender				0.37
Male (ref. group)	61.4	52.5	1	
Female	38.6	54	0.94 (0.82-1.07)	
Age groups				<0.0001*
18-34 (ref. group)	23.7	69.33	1	
35-49	29.8	56.48	0.76 (0.64-0.89)	
50-59	25.1	48.30	0.65 (0.55-0.78)	
60-64	10.2	43.59	0.60 (0.46-0.77)	
>65	11.1	29.00	0.39 (0.29-0.52)	
Deprivation category				0.6635
1 (ref. group)	5.0	50.00	1	
2	12.2	54.30	1.07 (0.76-1.52)	
3	24.7	50.13	0.97 (0.70-1.34)	
4	25.6	57.03	1.15 (0.84-1.59)	
5	14.1	52.56	1.05 (0.75-1.48)	
6	12.7	50.52	0.99 (0.70-1.40)	
7	5.7	55.17	1.09 (0.73-1.63)	
Transplant centre				<0.0001*
Centre 1 (ref. group)	16.9	52.32	1	
Centre 2	10.9	33.53	0.55 (0.41-0.74)	
Centre 3	18.7	59.09	1.19 (0.96-1.49)	
Centre 4	53.4	55.21	0.97 (0.81-1.18)	
Primary renal disease				0.0010*
Primary GN (ref. group)	25.9	62.27	1	
Interstitial nephritis	29.0	58.69	0.90 (0.76-1.06)	
Multisystem disease	15.3	42.30	0.71 (0.57-0.89)	
Diabetes	14.8	45.57	0.80 (0.64-1.00)	
Other/unknown	14.9	44.73	0.67 (0.54-0.83)	
Type of first dialysis				0.4014
Haemodialysis (ref. group)	60.0	52.24	1	
Peritoneal dialysis	40.0	54.42	1.06 (0.93-1.20)	
Distance to Tx centre				0.9768
<50 km	82.2	53.46	1	
50 – 100 km	8.2	51.2	1.02 (0.80-1.31)	
>100 km	7.7	53.39	0.99 (0.77-1.28)	
Time on dialysis pre-listing *(per year)*			0.85 (0.75-0.95)	0.0062*

Table 3.5 Socio-demographic, end-stage renal disease and geographic distribution of the waiting list population, proportion transplanted at three years after listing and the relative rates of transplantation for subgroups. (Univariate Cox regression analysis), (* statistical significant)

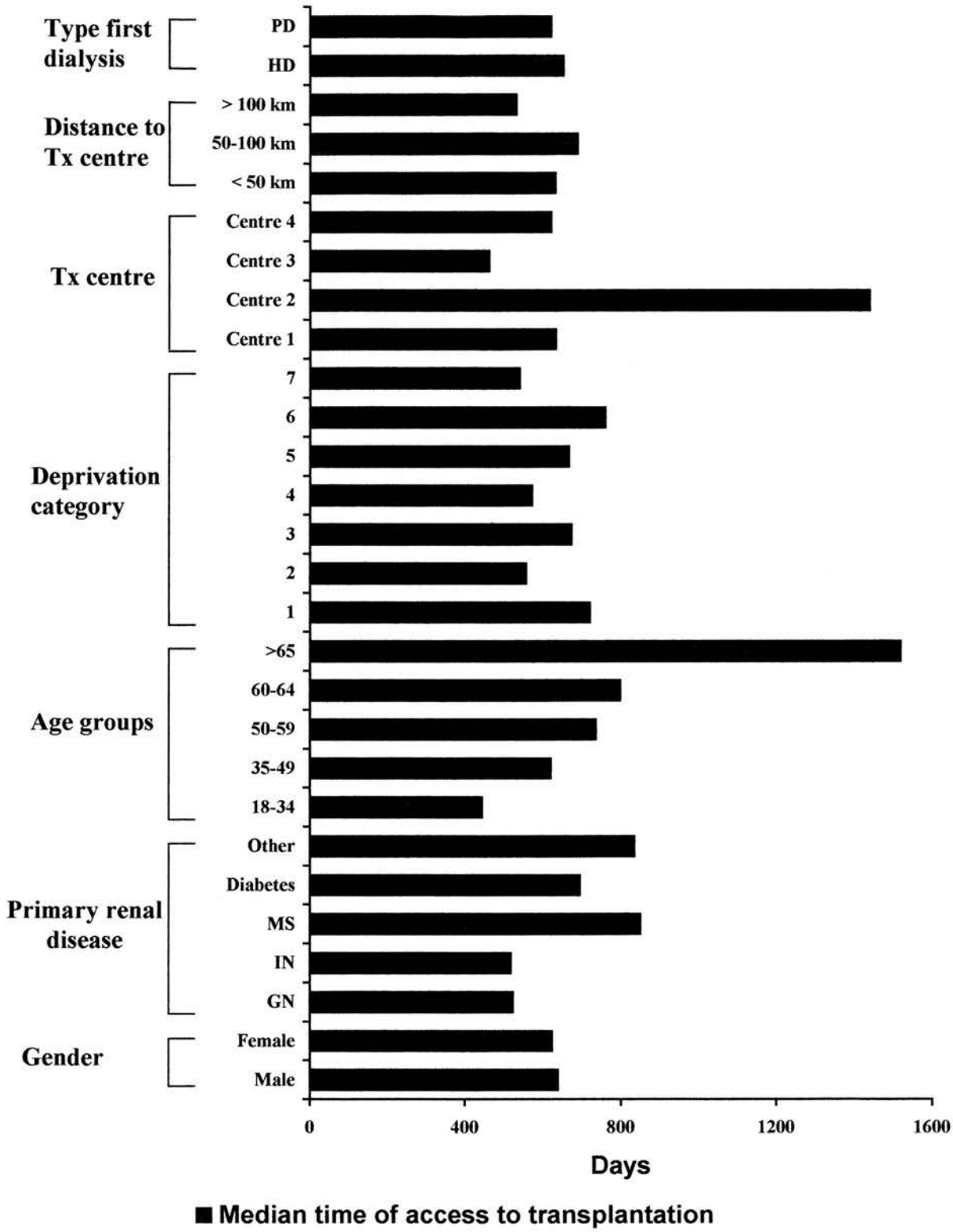


Figure 3.8 Median time of access to transplantation from listing (days) for each of the study variables

Multivariate analysis

A Cox regression model adjusted for all of the above variables and including the year of listing was developed. Patients over 65 years old have a 55% lower chance of transplantation compared with patients aged 18 to 34 years old, all covariates equal (table 3.6). The chance of transplantation decreases by 4% for each year closer to the end of the study. In a multivariate analysis, the time on dialysis pre-listing loses the statistical significance but there is a persistent centre effect.

	The relative risk (95% CI) of access to the transplantation	p value Cox regression
Age groups		
18-34 (reference group)	1	
35-49	0.77 (0.65 – 0.91)	0.0025
50-59	0.69 (0.57 – 0.83)	0.0001
60-64	0.64 (0.49 – 0.84)	0.0012
>65	0.45 (0.33 – 0.61)	<0.0001
Primary renal disease		0.0498
Primary GN	1	
Interstitial nephritis	0.90 (0.76 – 1.07)	0.2255
Multisystem disease	0.77 (0.62 – 0.97)	0.0278
Diabetes	0.81 (0.64 – 1.01)	0.0684
Other/unknown	0.75 (0.60 – 0.94)	0.0126
Listing transplant centre		
Centre 1 (reference group)	1	
Centre 2	0.57 (0.42 – 0.78)	0.0005
Centre 3	1.18 (0.92 – 1.51)	0.1838
Centre 4	0.92 (0.74 – 1.15)	0.4857
Year of listing, *per year*	0.96 (0.93 – 0.98)	0.0004

Table 3.6 Relative risks of access to transplantation (multivariate Cox proportional hazards model)

3.4 DISCUSSION

This longitudinal study demonstrates for the first time that there are significant differences in access to the renal transplant waiting list and renal transplantation in United Kingdom. Similar disproportions have been identified in USA, Canada and Europe (143;205;212-214) indicating that equity of access is a problem beyond the boundaries of a single transplant system.

Age has been identified in this analysis as a significant factor influencing the access to the renal transplant waiting list. Older patients are less likely to be listed, even after adjusting for all the other variables, listing rates declining by about 20% for each age group. Once a patient is listed, the same trend persists, elderly candidates being less likely to be transplanted, but the differences between the age groups are less prominent (figure 3.9).

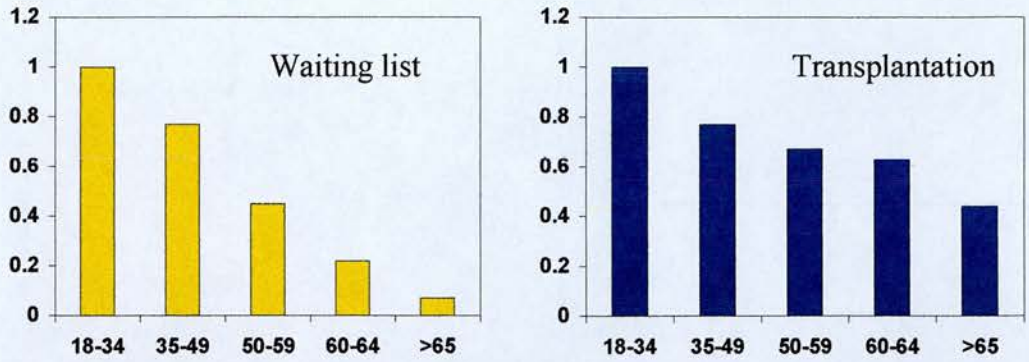


Figure 3.9 Relative waitlisting rates among incident dialysis patients and relative transplantation rates among listed dialysis patients, according to the age groups. Rates adjusted for age, gender, social deprivation, cause of ESRD, year of incidence and transplant centre

The sharper decline in access to the waiting list indicates that the main selection process takes place at the listing stage and may be attributable to the increased presence of comorbidity in the elderly, which may preclude them from being accepted as transplant candidates. Once listed, the difference is diminished as healthier candidates have already been selected and probably other additional factors such as the structure of the organ allocation system and decision making process influence the differences. The new donor organ allocation scheme introduced in UK in July 1998 (17) caters for equity of access by age, incorporating a donor-recipient age difference factor in the points scoring mechanism. There were insufficient data and length of follow-up in this study to allow for a comparison of the age differences in access to transplantation prior to and after the introduction of this new scheme. Other options, including separate allocation schemes for elderly and old-for-old

programmes have been implemented in other countries (Eurotransplant), with good results (215).

Gender is a significant determinant of access to the waiting list. We found that there is a 19% lower rate of listing for females than for males and this disparity is not due to age or socio-economic status, both variables being adjusted for in the multivariate analysis. A similar gender difference was reported previously (124;135) and strikingly similar rates of listing (RR=1 for males and RR=0.84 for females) were recently observed by Wolfe et al. in the USA in a national study (143). Several potential explanations for these differences have been advanced including patient preference (216), gender selection by health professionals (131;217), socio-economic and health status (134;218), non-compliance and gender-based differences in family preferences for transplant.

Once admitted onto the waiting list females have an equal probability of receiving a kidney transplant compared with males, after adjusting for all the other covariates. This finding suggests that the allocation system in place in UK may have eliminated gender differences, unlike other transplant programmes where a persistent gender disparity after listing is still noted (124;125;212).

The socio-economic status, assessed by deprivation scores (210), was found to be a significant predictor of access to the renal transplant waiting list. After adjustment for other factors, the listing rates decline the more deprived the patient. The reasons for these discrepancies rest with both patients and health professionals. Patients who are socio-economically disadvantaged may have a higher index of comorbidity,

while medical non-compliance may be more frequent in this group (18). It is conceivable that patients in this group may not appreciate the advantages of transplantation and as a result may not be good advocates for themselves when it comes to choosing the best treatment option. In addition, it is possible that health care workers may be biased to manage patients in ways that allow some to be listed sooner than others (146). Unlike other analyses (130), this study has shown that once listed, patients have an equal chance of transplantation, irrespective of their socio-economic status. This may indicate that most of the above potential reasons are eliminated with the assessment process prior to listing for transplantation.

Patients with diabetes and those with multisystem disease leading to ESRD have the lowest rate of listing for transplantation. When compared with primary glomerulonephritis patients and after adjusting for other factors, a patient with diabetes as primary renal disease has nearly half the rate of listing of a patient with GN. This may result from additional and more severe comorbidity that may preclude transplant candidacy. Once listed for transplantation, primary GN patients are the most likely to be transplanted. Although the rate of transplantation for diabetic patients is better than their rate of listing, the likelihood of further complications may be the underlying reason for the persisting differences in access to transplantation.

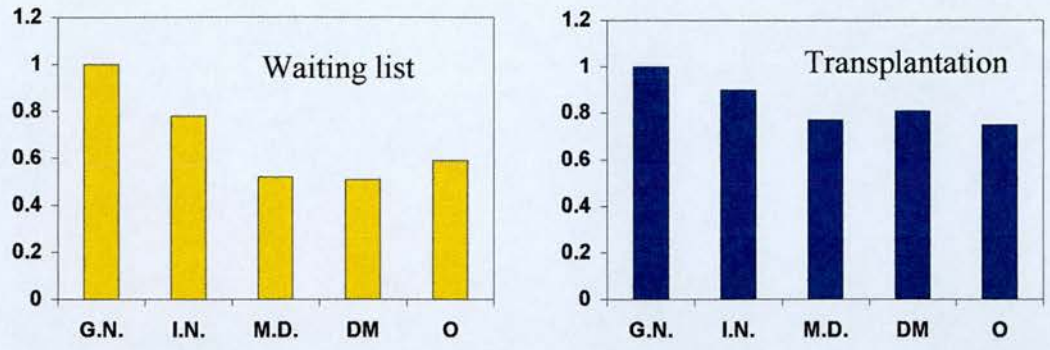


Figure 3.10 Relative waitlisting rates among incident dialysis patients and relative transplantation rates among listed dialysis patients, according to the primary renal disease (G.N. = primary glomerulonephritis, I.N. = interstitial nephritis, M.D. = multisystem disease, DM = diabetes mellitus, O = other/unknown). Rates adjusted for age, gender, social deprivation, cause of ESRD, year of incidence and transplant centre

The type of 1st RRT (peritoneal dialysis versus haemodialysis) was found to be a significant predictor of access to the waiting list, patients starting RRT on PD being more likely to be listed. Although this variable was included in the final model, one must interpret its significance with caution, for various reasons. The type of first renal replacement therapy is chosen according to the patient's general status, primary disease, tolerance or preference. Furthermore, there are a significant number of patients who will switch between therapeutic modalities (up to six times in the present cohort) throughout the course of their treatment and therefore a proper analysis of the impact of dialysis modality on access to the waiting list should include not only the type but also the length of time spent on each modality.

A longer waiting time on dialysis pre-transplantation has recently been correlated with a poorer outcome. In a multivariate analysis, Meier-Kriesche (47) noted a substantial reduction in the success rate of a kidney transplant, the longer the time on dialysis, suggesting that once patients reach the end stage of the renal disease, they should be transplanted as early as possible. In the multivariate analysis, we found no correlation between the chances of transplantation and the length of time spent on dialysis pre-listing suggesting no discriminatory effect against those referred later in the course of their renal disease.

Differences in access according to geographical criteria have been previously reported (208). A univariate analysis of the linear distance between the patient's home and the transplant centre revealed a surprising finding. The further away from the transplant centre the patients lived the quicker the access to the waiting list. The distance factor remained a predictive variable of access to the waiting list, even after adjustment for the transplant centre to which the patient was referred.

To investigate the centre effect, two different models were built. The first one, including all the socio-demographic variables and grouping the patients by the proximity of the dialysis unit with a transplant centre found that patients starting RRT in a renal unit, which is in the same hospital with a transplant unit, have a 28% better listing rate than patients dialysed elsewhere. The second model included the same socio-demographic indicators and grouped the patients according to the transplant centre to which they are referred depending on the geographical allocation

of the renal units to a transplant centre. There seems to be a persistent centre effect both for access to the waiting list and access to transplantation as shown in figure 3.11. On close analysis, the effect on access to transplantation was mainly due to one centre with significant longer waiting time and lower chances of transplantation for listed patients. Hence, it would be fair to say that the centre effect on access to transplantation is artificial and is due to the outlying effect of this particular centre.

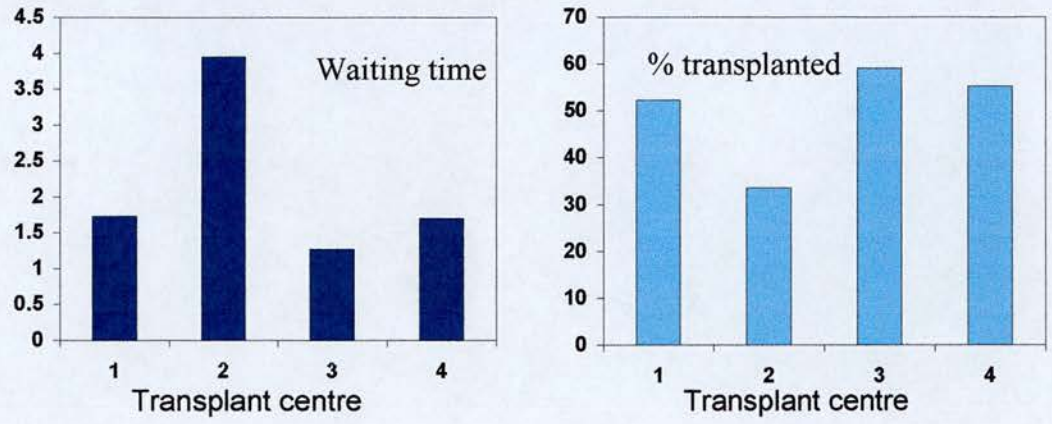


Figure 3.11 % patients transplanted and length of waiting time from listing to transplantation (years) in each transplant centre in Scotland 1989-1999.

We can only speculate about the reasons behind these transplant or renal unit differences, but it has been suggested that centre characteristics (126), renal unit size and organizational aspects (131), health care staff attitudes towards transplantation (199;200) and training may affect transplant status. Clinical practice guidelines in the evaluation of renal transplant candidates have been introduced in USA (18) and suggested in Europe (157) and may help to eliminate the centre effect.

Comorbidity may account for some of the differences highlighted here. This analysis is based on all incident adult patients that started RRT between 1989 and 1999 and comorbid conditions were not available throughout this period, so their effect could not be examined. However, there is evidence from the USA (130), where similar inequities of access were noted, that the addition of the comorbid factors in the analysis does not alleviate the effects of the sociodemographic variables and only modestly improves the predictive power of the model.

Racial differences in access to transplantation have been documented for over a decade (126;132;207;219). The lack of ethnic origin details in the Scottish Renal Registry and UK Transplant database for the study period did not allow us to undertake such an analysis.

In the absence of a way to identify patients who will never be suitable for listing and transplantation at the time when RRT is begun, the median time of access to the waiting list was calculated on an "intention to treat" basis. Although statistically correct, this method, produces long waiting times which give little information of clinical value when one is interested in the time taken to listing for a patient who is obviously fit for transplantation. This is compounded in certain categories because a large proportion of patients in these categories are never listed. Therefore, a separate analysis, taking into account only those patients listed within the study period, irrespective of their length of follow-up, was carried out. This analysis, although in statistical terms in danger of bias, gives an indication of the actual time taken for assessment and listing in the different categories (data shown on page 116, table 3.3).

Of the 408 cases excluded from the analysis, 167 patients were removed as they were listed prior to starting dialysis and they could not be fitted in these models, which include age at the beginning of RRT (for access to the waiting list) and time on dialysis pre-listing (for access to transplantation). 44 of these cases were transplanted pre-emptively while the remaining patients spent some time on dialysis before receiving a kidney transplant. However, separate analyses, which include these cases, were carried out and produced identical results with the models presented in this study (data shown in table A.14, appendix, page 346 and table A.15, appendix, page 347).

A sequence of potential barriers along the clinical pathway to transplantation has been documented (123). Our study has shown that for some of the factors, like gender and socio-economic status, the barrier seems to be at the listing stage rather than transplantation, while for other, like age and primary renal disease the differences persist at both steps. The current data did not allow exploration of the various issues, which may explain these differences, and therefore studies designed to address these factors are needed.

3.5 CONCLUSION

In summary, for whatever reasons, there appear to be inequities in access to the renal transplant waiting list and renal transplantation in Scotland. Since the management of end stage renal failure, referral pattern for transplantation and the transplantation process itself are similar throughout the UK, it would be surprising if these inequities do not exist in other parts of Britain. The explanation of these differences is complex and warrants further investigation.

It is important that patients with advanced renal disease and those who care for them are aware of the factors associated with successful listing and transplantation. The transplant community often concentrates on graft and patient survival rates following a transplant procedure and there is no doubt from this study that transplantation provides the best outcome (figure 3.12).

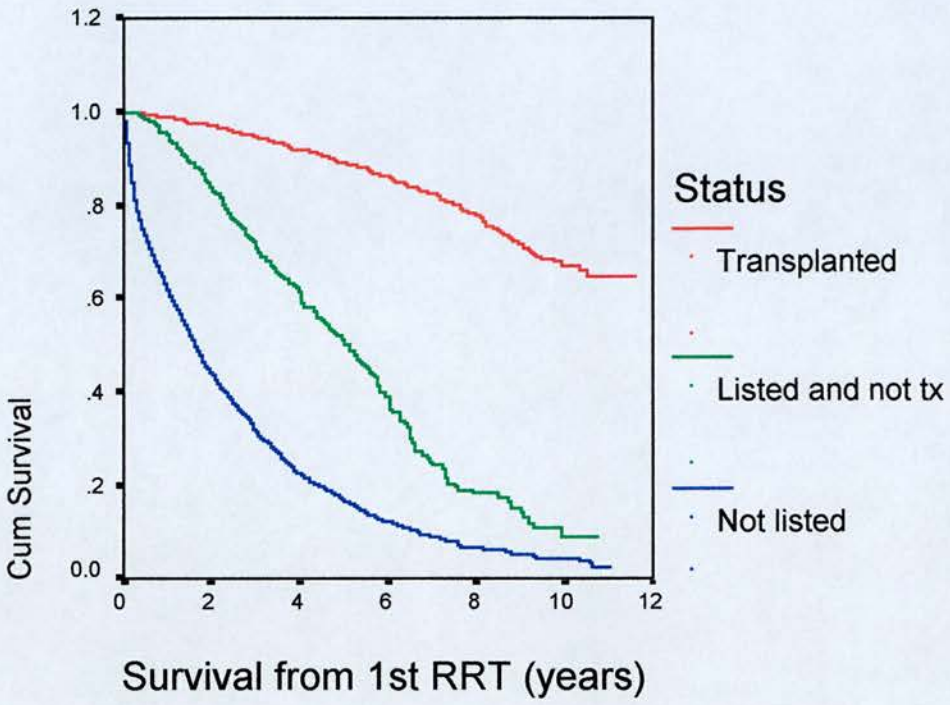


Figure 3.12 Patient survival in Scotland according to the treatment status (1989-1999).

These findings are equally important from the public's point of view. A system that does not grant access to transplantation to all patients that need it will be viewed as an unfair system. The perception of inequity threatens the very foundation upon which altruistic donation and transplantation are built and therefore fairness in access should be pursued with the same dedication with which we seek new immunosuppressive medication or better dialysis regimens.

CHAPTER 4

IMPACT OF COMORBIDITY ON ACCESS TO THE RENAL TRANSPLANT WAITING LIST AND RENAL TRANSPLANTATION IN SCOTLAND

4.1 INTRODUCTION

The differences in access to the transplant waiting list and renal transplantation highlighted in the previous chapter are very important for both health care professionals and end-stage renal disease patients. Some of the results (*e.g.* differences in access to the waiting list by gender) are intriguing and difficult to interpret, while others (*e.g.* differences in access by age groups) were more predictable.

The main factor, which has not been included in the analysis and is believed to have a major impact on the prognostic value of the proposed model is comorbidity. The difficulties in building a complex model including comorbidity are multiple. First of all, collecting accurate data may prove to be a difficult and daunting task, as there is no computerised database containing this information, and retrieving case notes to obtain retrospective data is time consuming and exposed to bias. Secondly, there is no agreement on what comorbidity – if any – should be recorded in a database. Thirdly, there are limited data on the impact of comorbidity on a patient's chances of being listed or transplanted. Finally, a prospective data collection is the desired approach, but this requires significant financial and human resources.

Not surprising, even the largest analysis to date, which investigates differences in access to renal transplantation in over a quarter of a million patients in the US (143) has used only a sociodemographic model. It is widely accepted that these sort of analyses are useful, but they are not perfect. Recognizing these weak points, a series

of papers (130;131), have included comorbidity in a predictive model for access to transplantation, but none of them gives a national perspective or collects data prospectively at the moment of 1st RRT, listing and transplantation. Interestingly, Gaylin et al. showed that the addition of comorbidity does improve the predictive power of the model, but only by a small margin, without diminishing the predictive value of the sociodemographic variables.

To address these issues and to investigate the impact of comorbid conditions on the access to renal transplant waiting list and renal transplantation in Scotland, an analysis was performed on patients listed for transplantation for which comorbidity was collected from case notes review and combined with sociodemographic data from the SRR and UKT. The questions were whether comorbidity accrued until the time of listing influences:

i) the speed of access to the waiting list and

ii) access to transplantation.

4.2 METHODS

4.2.a Patient population

As shown in the previous chapter, 1736 adult patients started dialysis and were listed for transplantation between 1st of January 1989 and 31st of December 1999. A single investigator visited all four transplant centres and collected the comorbidity data from patients' notes. 1022 case notes were available for investigation. The remaining 714 were destroyed (deceased patients, or not in the care of the unit for more than 5 years), missing, or unavailable. In total, data was collected for 58.9% of all listed patients.

An extensive amount of data on all comorbid conditions accumulated by a patient prior to listing was collected for each patient on a pro-forma (appendix, page 348-351). Comorbid conditions listed included:

- Diabetes
- Peripheral vascular disease
- Hypertension
- Ischaemic heart disease
- Left ventricular function
- Respiratory disease
- Cerebrovascular disease

- Hepatic function
- GI disorders
- Urology disorders

Each comorbid condition was recorded only if a diagnosis was ascertained and not just based on the presence of symptoms. The findings of all the investigations (X-ray, ECG, cardiac echography, HLA grouping, lymphocytotoxic antibodies analysis, blood group and other blood tests) were recorded from the appropriate forms. For some of the comorbid conditions (*e.g.* diabetes, ischaemic heart disease, peripheral vascular disease, heart failure, respiratory disease, cerebro-vascular disease, GI and urological disorders) extensive details of the type and stage of disease and complications were collected (appendix, page 348-351) (*e.g. Claudication, ischaemic ulcer/rest pain, revascularisation, amputation* for **peripheral vascular disease,** *type of diabetes, number of end-organ complications* for **diabetes**).

The data was than fitted in a database containing sociodemographic factors, indicators of renal disease and dialysis as well as listing, transplant and donor information retrieved from the SRR and UKT.

4.2.b Statistical analyses

Most of the comorbid conditions examined in this analysis have been shown to be positively correlated with mortality (220). Therefore, some of them, might be negatively associated with transplantation, simply because patients with these conditions are likely to die before they are listed or receive a transplant. As a result, the primary analysis method employed a time to event proportional hazards regression (221) where the event analysed was i) listing for transplantation and ii) transplantation. This method uses the information on whether a patient is listed/transplanted and also incorporates the time between the start of dialysis therapy and the eventual end point (if one occurred), death or end of the analysis period. That is, if patients die, they are removed from the analysis (censored) at the time of death, and the mortality risk of the comorbid conditions does not "compete" with the likelihood of listing/transplantation.

The models were adjusted for all sociodemographic factors described in chapter 4 (age, gender, social deprivation, primary renal disease, type and year of first dialysis, transplant centre, distance from patient's home to the transplant centre), to eliminate the potential differences in the distribution of diseases across these groups. The univariate models were built in a standard entry manner to identify the significant variables. Statistical significance of individual factors was evaluated with a Wald statistic. Probability values of 0.05 or less were considered statistically significant for this analysis.

The multivariate model was built in a step-wise forward selection manner, which includes only those variables with significant influence in a univariate analysis. A level of significance of 0.10 was chosen as a cut-off point to ensure that all factors with a significant impact are included in the analysis. In addition, this method eliminates the potential interaction, which may occur when factors are highly co-linear.

4.2.c Outcome

As all patients in this analysis were listed, the impact of comorbidity on the rates of listing could not be evaluated (no data available for not-listed patients). However, using comorbidity accrued until listing, an investigation could be undertaken into whether there are any differences in the speed of access to the waiting list between patients with different levels of comorbidity.

In the second part of the analysis, the impact of each comorbid factor on the rates of access to transplantation was determined, as data was available for both transplanted and censored patients (on dialysis).

In addition, a comparison between the median times of access to the waiting list and transplantation for patients with any given comorbid condition and those where the condition was absent was carried out.

Finally, a comparison between the predictive power of a basic socio-demographic model as proposed in Chapter 4 and a more complex model including comorbidity was performed.

4.3 RESULTS

4.3.I Access to the waiting list

Univariate analysis

Table 4.1 illustrates the impact of cardiovascular comorbid conditions on the speed of access to the waiting list, compared with patients where such conditions are absent (relative risk = 1, reference).

Factor	Condition present Relative risk	95% CI	p value
Peripheral vascular disease	0.795	0.651-0.969	0.023*
Hypertension	1.337	1.095-1.632	0.004*
Ischaemic heart disease	0.800	0.679-0.943	0.008*
Valvular disease	0.867	0.737-1.019	0.083**
Pulmonary embolism	0.695	0.409-1.181	0.178
Cardiac arrhythmias	0.865	0.646-1.157	0.329
Heart failure	0.717	0.555-0.927	0.011*
Ventricular function impairment	0.992	0.928-1.061	0.822
Left ventricular hypertrophy	0.866	0.750-1.000	0.050*
Other cardiac conditions	0.873	0.721-1.057	0.165
Cardiac arrest	0.858	0.659-1.117	0.256

Table 4.1 Impact of cardiovascular comorbid conditions on the speed of access to the waiting list (condition absent = reference group). (* = statistical significant at a level of 0.05, ** = significant at a level of 0.10)

Patients with heart failure spend a significantly longer time on dialysis pre-listing compared with patients with normal heart function (RR = 0.717, p = 0.011). A similar trend is noted for patients with left ventricular hypertrophy, ischaemic heart disease and peripheral vascular disease while only a marginal effect (p = 0.083) is noticed for those with valvular disease. These patients are likely to require additional investigations prior to being considered suitable transplant candidates. Hypertension is a frequent problem in end stage renal failure patients and is ubiquitous in the advanced stages of the disease. Interestingly, these patients tend to be listed faster, indicating that most patients in the advanced stages of the disease are referred for transplantation.

The presence of other comorbid conditions (table 4.2) has a significant impact on how quickly patients will be listed. Respiratory diseases (*e.g.* asthma, COAD, emphysema, bronchitis) and previous cerebrovascular problems (*e.g.* transient ischaemic attacks, cerebro-vascular accidents, hypertensive encephalopathy) significantly lengthen the time a patient takes to be admitted on the waiting list (RR= 0.727, 95%CI: 0.601-0.879 and RR= 0.769, 95%CI: 0.617-0.959 respectively). Patients with previous neoplasia are admitted on the waiting list, but as expected, they will wait significantly longer (RR=0.550, 95%CI: 0.349-0.869) before doing so, as most transplant centres will require a minimum period of 3-5 years of disease free period, before exposing a cancer patient to the risk of immunosuppression.

Other conditions with a statistical significant impact on the speed of access to the renal waiting list include a history of diabetes which does not lead to renal failure

(RR = 0.569, p = 0.004) and a history of gastrointestinal disorders (duodenal ulcer, gastric ulcer, GI bleed, GORD, surgery for any of these) (RR = 0.834, p = 0.024).

Factor	Condition present Relative risk	95% CI	p value
Diabetes as a comorbid disease	0.569	0.387-0.837	0.004*
Respiratory disease	0.727	0.601-0.879	0.001*
Cerebrovascular disease	0.769	0.617-0.959	0.020*
Positive hepatic virology	0.998	0.801-1.243	0.984
Alcoholic liver disease	1.148	0.878-1.501	0.314
Ascites	1.055	0.759-1.466	0.752
Cirrhosis	0.624	0.156-2.501	0.506
Neoplasia	0.550	0.349-0.869	0.010*
GI disorders	0.834	0.712-0.977	0.024*
Urological problems	0.894	0.743-1.076	0.236
Hyperlipidaemia	0.913	0.779-1.070	0.259
Active smoker	0.967	0.818-1.144	0.698
Ex-smoker	0.939	0.787-1.120	0.483
BMI	0.994	0.980-1.008	0.383
Hyperparathyroidism	0.953	0.869-1.044	0.303

Table 4.2 Impact of other comorbid conditions on speed of access to the waiting list (condition absent = reference group, RR=1). (* = statistical significant at a level of 0.05, ** = significant at a level of 0.10)

Patients wait for disproportionate lengths of time prior to being listed, depending on their blood groups. Patients with blood group O and AB have the fastest access to the list, while patients with blood group B seem to wait significantly longer, as shown in table 4.3.

Factor	Relative risk	95% CI	p value
Blood group O	1		
Blood group A	0.982	0.845-1.140	0.810
Blood group B	0.802	0.645-0.998	0.048*
Blood group AB	1.190	0.806-1.755	0.382

Table 4.3 Impact of patient's blood group on speed of access to the waiting list (blood group O = reference group). (* = statistical significant at a level of 0.05)

Some of these comorbid conditions may have an overlapping effect as well as an unequal distribution among different age groups, social deprivation or gender populations. Therefore, we conducted a multivariate analysis adjusted for socio-demographic variables, which included the comorbid conditions identified as significantly influencing the speed of access to the waiting list in the univariate analysis.

Multivariate analysis

The results of the multivariate analysis are presented in table 4.4. After adjustment for all the covariates, female patients have a 28% lower chance of being listed in an equal length of time with males (RR=0.813, 95%CI: 0.695 – 0.952).

Even in patients considered suitable candidates for transplantation, there are significant differences in the speed of access to the waiting list by age, younger patients being listed faster than older patients.

Overall, deprivation category has a significant impact on the speed of access to the waiting list ($p= 0.002$), but on close analysis, most patients spend similar lengths of time on dialysis pre-listing, irrespective of their deprivation category, when compared with group one (the least deprived patients) taken as reference group.

All patients are listed in similar intervals of time irrespective of how far away they live from the transplant centre. However, there is a significant centre effect ($p<0.0001$), patients referred to centre 4 waiting longest prior to being listed (RR = 0.550, 95%CI: 0.434 – 0.697).

There is a significant disproportion in the time taken to listing according to the primary renal disease ($p=0.0002$), patients with multisystem disease and those with diabetes as a cause of renal failure waiting significantly longer to be listed, compared with patients with glomerulonephritis.

Factor	RR	95%CI	p value
Gender *Female vs. male*	0.813	0.695 – 0.952	0.010
Age groups			<0.0001
18-34	1		
35-49	0.919	0.754 – 1.120	0.401
50-59	0.641	0.517 – 0.794	<0.0001
60-64	0.630	0.478 – 0.832	0.001
>65	0.467	0.356 – 0.614	<0.0001
Deprivation category			0.002
1	1		
2	1.386	0.969 – 1.982	0.074
3	1.124	0.798 – 1.583	0.505
4	0.991	0.707 – 1.387	0.956
5	0.781	0.533 – 1.145	0.206
6	0.785	0.542 – 1.137	0.200
7	0.928	0.608 – 1.416	0.728
Transplant centre			<0.0001
Centre 1	1		
Centre 2	0.973	0.740 – 1.278	0.842
Centre 3	0.646	0.505 – 0.827	0.001
Centre 4	0.550	0.434 – 0.697	<0.0001
Primary renal disease			0.004
Primary GN	1		
Interstitial nephritis	0.977	0.795 – 1.201	0.827
Multisystem disease	0.686	0.548 – 0.859	<0.0001
Diabetes	0.761	0.602 – 0.963	0.023
Other	0.837	0.653 – 1.073	0.160
Type first dialysis *(PD vs. HD)*	1.378	1.178 – 1.611	<0.0001
Diabetes as a comorbid condition	0.687	0.454 – 1.040	0.076‡
Hypertension	1.412	1.136 – 1.756	0.002
LVH	0.843	0.720 – 0.987	0.034
CVD	0.786	0.621 – 0.994	0.045
Respiratory disease	0.804	0.652 – 0.991	0.041
Neoplasia	0.583	0.356 – 0.952	0.031
Urological pathology	0.812	0.655 – 1.006	0.057‡

Table 4.4 Impact of comorbidity conditions and demographic variables on the speed of access to the waiting list (relative risk, patients without comorbid condition = reference group), (‡ significant at p=0.10)

Of the cardiovascular comorbid conditions with a statistical significant effect in a univariate analysis only left ventricular hypertrophy and hypertension retain their impact in a multivariate analysis (table 4.4). The other factors (peripheral vascular disease, ischaemic heart disease and heart failure) do not reach statistical significance in this model, probably due to their association with other, more predictive factors.

The presence of respiratory disease, cardiovascular problems or previous neoplasia has a major impact even after adjustment for all the other covariates in the model. Marginally significant adverse effects on access to the transplant waiting list are noted for patients with diabetes as a comorbid disease (RR = 0.687, p = 0.076) and those with urological disorders (*e.g.* neurological bladder, congenital abnormalities, nephrectomies, ileal conduit) (RR = 0.812, p = 0.057). The effect of this later factor must be interpreted with care. As no significant effect was observed in the univariate analysis, the marginal effect noticed in the multivariate analysis may be due to an interaction with other factors in the model.

Comparison of demographic and comorbidity adjusted models

The model presented above, adds the comorbidity conditions to the sociodemographic covariates of the model presented in Chapter 4 (gender, age, deprivation category, primary renal disease, type and year of first dialysis, transplant centre and distance from patient's home to the transplant centre). Overall, the

addition of these factors improves the model's predictive power of the speed of access to transplantation by about 8% (-2Log likelihood 9028.301, $p<0.0001$, $df=28$). An examination of the relative rates for different groups of patients in the two models (table 4.5) shows that including the comorbid conditions does not change substantially the effects of each of the basic sociodemographic model variables.

Female patients, older patients, diabetics and patients with multisystem disease as well as patients starting RRT on haemodialysis will wait longer prior to being listed compared with the other patients that are listed.

A more complex model including all 25 comorbid conditions presented in table 4.1 and 4.2 rather than just those with significant impact on access to the waiting list, showed no significant changes in the coefficients of the sociodemographic variables, and therefore was not utilised.

Factor	Basic sociodemographic model		Model adjusted for comorbidity	
	RR	p value	RR	p value
Gender				
Male	1		1	
Female	0.830	0.013	0.813	0.010
Deprivation score				
1	1		1	
2	1.356	0.082	1.386	0.074
3	1.185	0.301	1.124	0.505
4	1.012	0.942	0.991	0.956
5	0.808	0.242	0.781	0.206
6	0.811	0.235	0.785	0.200
7	0.885	0.547	0.928	0.728
Age groups				
18-34	1		1	
35-49	0.945	0.555	0.919	0.401
50-59	0.628	<0.0001	0.641	<0.0001
60-64	0.610	<0.0001	0.630	0.001
>65	0.480	<0.0001	0.467	<0.0001
Primary renal disease				
Glomerulonephritis	1		1	
Interstitial nephritis	0.899	0.270	0.977	0.827
Multisystem disease	0.648	<0.0001	0.686	0.001
Diabetes	0.784	0.035	0.761	0.023
Other	0.821	0.101	0.837	0.160
Transplant center				
1	1		1	
2	0.920	0.532	0.973	0.842
3	0.613	<0.0001	0.646	0.001
4	0.567	<0.0001	0.550	<0.0001
Distance to Tx centre				
<50 km	1		1	
50-100 km	0.962	0.775	0.964	0.796
>100 km	0.772	0.293	0.886	0.639
Type first dialysis				
Haemodialysis	1		1	
Peritoneal dialysis	1.423	<0.0001	1.378	<0.0001
Year of first dialysis				
per year	0.998	0.846	1.000	0.996

Table 4.5 Sociodemographic and comorbidity factors and impact on the speed of access to the renal transplant waiting list – comparison of a basic demographic and comorbidity adjusted models

An analysis of the length of time to listing shows that patients considered suitable for transplantation wait on average 157 days from the moment they start dialysis until they are listed. The comorbidity load exhibited by a particular patient may modify this interval by a significant margin.

The presence of most cardiovascular conditions requires an additional 10 - 20 days prior to the patient being listed (figure 4.1), with the exception of hypertensive patients who tend to be listed quicker than those with normal blood pressure.

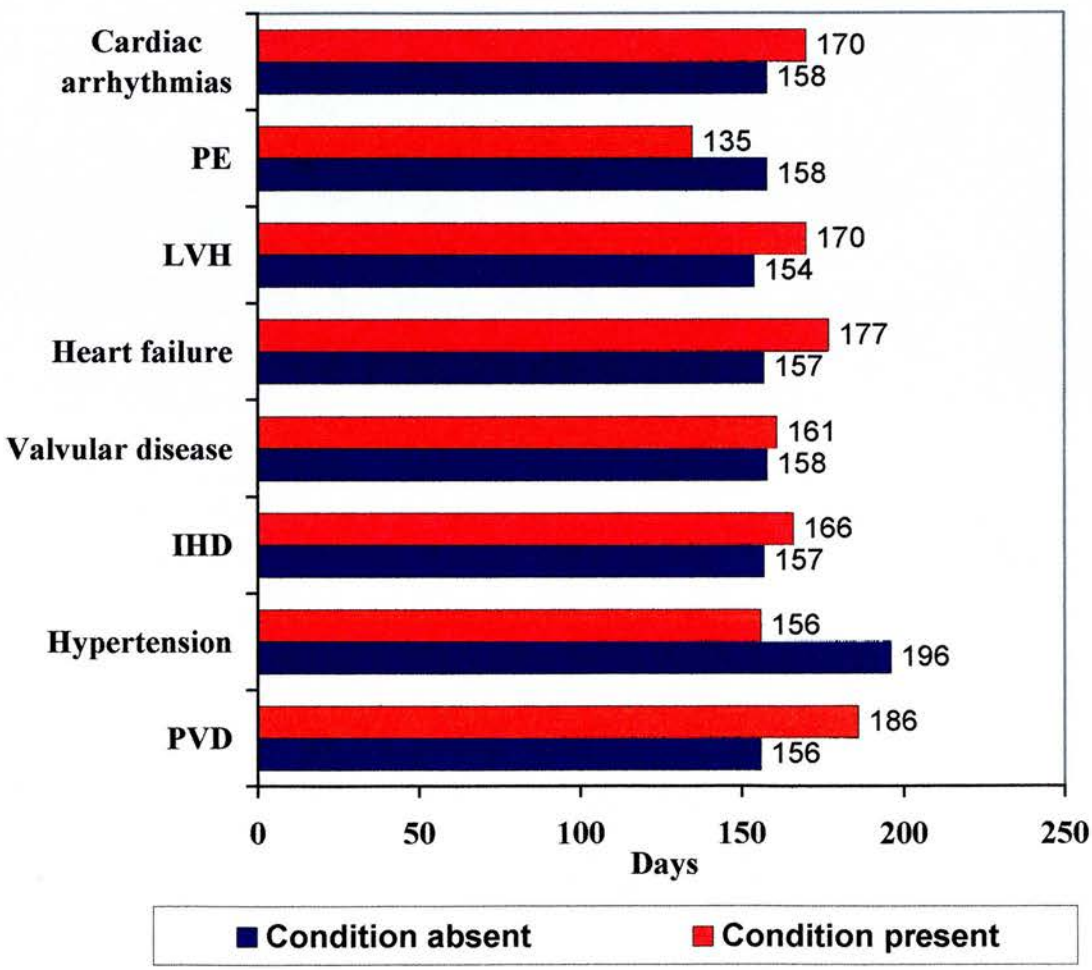


Figure 4.1 Median time of access to the waiting list from first RRT for patients with cardiovascular comorbidity (adjusted for all sociodemographic and comorbid variables)

As expected, previous neoplasia will lengthen the time on dialysis pre-listing by 75% (figure 4.2), as a minimum of 3-5 years free of disease are required prior to the patient being at risk of recurrence under immunosuppressive medication. The presence of other serious comorbid conditions such as diabetes (not leading to renal failure), cerebro-vascular or respiratory diseases increases the waiting time by 20 - 30%, while for other conditions such as hyperlipidaemia and gastrointestinal disorders, the increase is more modest.

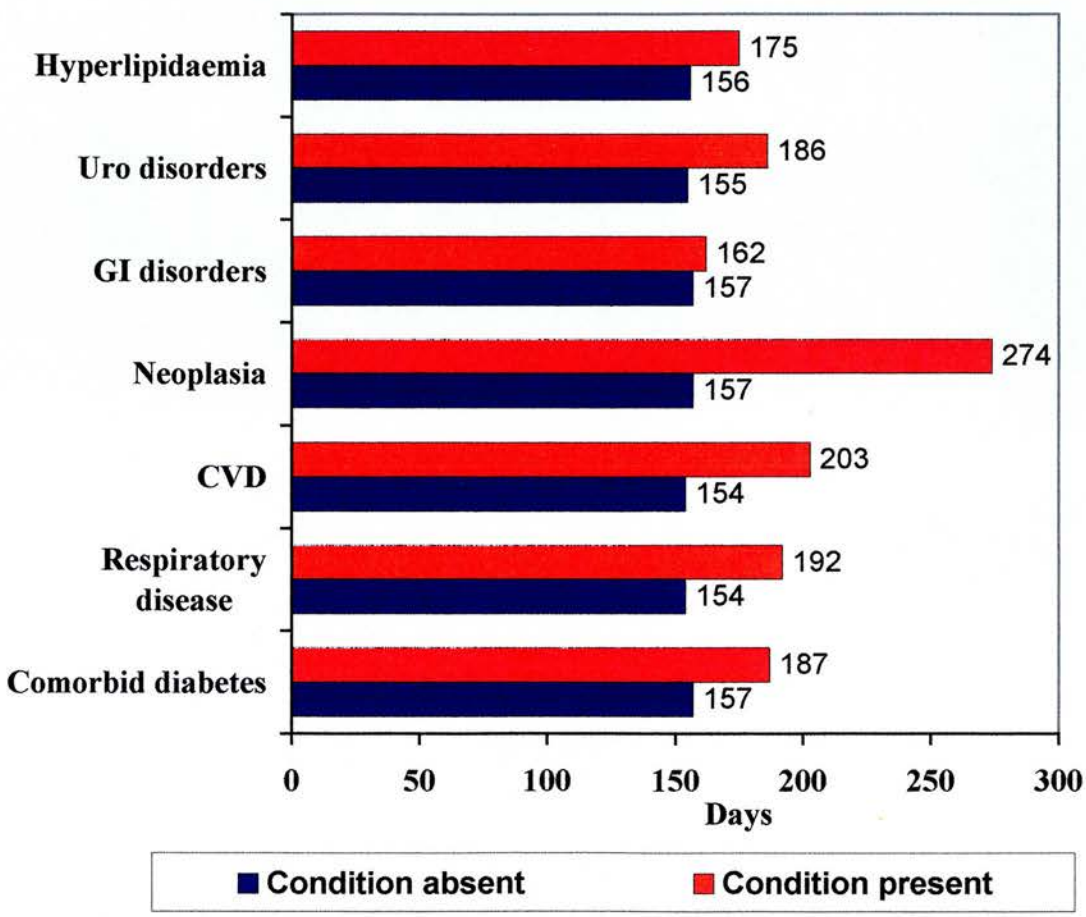


Figure 4.2 Median time of access to the waiting list from first RRT for patients with various comorbid conditions (adjusted for all sociodemographic and comorbid variables)

4.3.II. Access to transplantation

Univariate analysis

Data was available for transplant recipients as well as patients who remained on the waiting list by the end of the study period. Therefore it was possible to determine not only the impact of the variables on the time of access to transplantation, but more important, the impact on the likelihood of receiving a kidney, once admitted onto the waiting list.

The influence of the individual cardiovascular comorbid conditions on access to transplantation is shown in table 4.6. Cardiac arrhythmias seem to be the most significant factor, their presence reducing the chances of transplantation by about 50% (RR=0.459, 95%CI: 0.283-0.744). There is a 30% lower chance of transplantation for patients who have peripheral vascular disease or ischaemic heart disease when listed (RR=0.702, 95%CI: 0.526-0.937 and RR=0.701, 95%CI: 0.555-0.885 respectively) compared with those free from these diseases. Patients with left ventricular hypertrophy are also less likely (RR=0.814, 95%CI: 0.676-0.980) to be selected as recipients when a kidney becomes available, while the presence of other cardiovascular conditions such as heart failure, previous cardiac arrests or hypertension has no impact on the likelihood of transplantation.

Factor	Condition present Relative risk	95% CI	p value
Peripheral vascular disease	0.702	0.526 - 0.937	0.016*
Hypertension	0.926	0.724 - 1.185	0.543
Ischaemic heart disease	0.701	0.555 – 0.885	0.003*
Valvular disease	0.834	0.655 – 1.061	0.139
Pulmonary embolism	1.307	0.676 – 2.528	0.426
Cardiac arrhythmias	0.459	0.283 – 0.744	0.002*
Heart failure	0.971	0.679 – 1.388	0.870
Ventricular function impairment	0.995	0.922 – 1.073	0.889
Left ventricular hypertrophy	0.814	0.676 – 0.980	0.030*
Other cardiac conditions	0.947	0.755 – 1.188	0.636
Cardiac arrest	0.937	0.700 – 1.254	0.661

Table 4.6 Impact of cardiovascular comorbid conditions on the rate of access to transplantation (condition absent = reference group). (* = statistical significant at a level of 0.05)

Other comorbid conditions with a significant impact on transplantation rates are a history of gastrointestinal pathology (*e.g.* gallstones, ulcers, previous GI bleed, GORD) (RR= 0.763, 95%CI: 0.619 – 0.942), hyperparathyroidism (RR= 0.871, 95%CI: 0.760-0.997) and cessation of smoking prior to listing (table 4.7).

Factor	Condition present Relative risk	95% CI	p value
Diabetes as a comorbid disease	0.896	0.527 - 1.524	0.686
Respiratory disease	0.912	0.712 – 1.169	0.469
Cerebrovascular disease	0.939	0.698 – 1.263	0.678
Positive hepatic virology	0.730	0.476 – 1.120	0.149
Alcoholic liver disease	1.002	0.653 – 1.537	0.994
Ascites	0.950	0.582 – 1.549	0.836
Cirrhosis	3.693	0.919 – 14.845	0.066
Neoplasia	0.927	0.523 – 1.643	0.795
GI disorders	0.763	0.619 – 0.942	0.012*
Urological problems	1.091	0.867 – 1.374	0.457
Hyperlipidaemia	0.913	0.779 – 1.070	0.259
Active smoker	1.126	0.918 – 1.381	0.256
Ex-smoker	0.739	0.583 – 0.937	0.013
BMI	0.990	0.973 – 1.007	0.244
Hyperparathyroidism	0.871	0.760 – 0.997	0.045*

Table 4.7 Impact of other comorbid conditions on the rate of access to transplantation (condition absent = reference group). (* = statistical significant at a level of 0.05)

There are significant differences in the likelihood of transplantation depending on recipients' blood group (table 4.8). As kidney transplants are performed in blood group matched recipients, these differences may reflect not only recipient causes, but more likely a disproportion in the distribution of blood groups amongst donors.

Factor	Relative risk	95% CI	p value
Blood group O	1		
Blood group A	1.471	1.226 – 1.766	<0.0001
Blood group B	1.067	0.804 – 1.417	0.653
Blood group AB	2.799	1.806 – 4.338	<0.0001

Table 4.8 Impact of recipient blood group on the likelihood of transplantation

Multivariate analysis

Leaving aside those factors with a potential donor correlation (blood groups), all recipient demographic and comorbidity factors were included in a multivariate model. After adjusting for all the covariates, only the factors shown in table 4.9 retain a significant impact on the chances of receiving a kidney graft. Once listed, patients have comparable chances of being transplanted irrespective of their gender, age, deprivation category, or primary renal disease. The type of dialysis and the time spent on dialysis pre-listing have no impact on the chances of receiving a kidney transplant, but there is a 4% (RR= 0.961, 95%CI: 0.928 – 0.994) lower transplantation rate for each listing year closer to the end of the study.

There seem to be a persistent centre effect, but this is likely to be due to the outlying value of centre 2, where patients, once listed, have a lower rate of transplantation compared with the remaining centres (RR=0.464, 95%CI: 0.320 – 0.673).

Of all the comorbid conditions significantly associated with lower transplantation rates in a univariate analysis, only the presence of cardiac arrhythmias and hyperparathyroidism reached statistical significance in the multifactorial Cox model.

Factor	Relative risk	95%CI	p value
Year of listing, *per year*	0.961	0.928 - 0.994	0.022
Tx centre			<0.001
Centre 1	1		
Centre 2	0.464	0.320 - 0.673	<0.001
Centre 3	1.309	0.979 - 1.750	0.069
Centre 4	0.911	0.680 - 1.222	0.535
Cardiac arrhythmias	0.531	0.318 – 0.886	0.015‡
Hyperparathyroidism	0.785	0.655 – 0.940	0.009‡

Table 4.9 Impact of demographic and comorbidity variables on access to transplantation (multivariate analysis; ‡ compared with cases where condition is absent)

Comparison of demographic and comorbidity adjusted models

The addition of comorbid diseases to a predictive model for access to transplantation produces significant changes in the model (table 4.10).

Factor	Basic sociodemographic model		Model adjusted for comorbidity	
	RR	p value	RR	p value
Gender				
Male	1		1	
Female	0.962	0.669	0.971	0.762
Primary renal disease				
Glomerulonephritis	1		1	
Interstitial nephritis	0.810	0.058	0.804	0.067
Multisystem disease	0.790	0.092	0.780	0.099
Diabetes	0.754	0.064	0.790	0.142
Other	0.643	0.004	0.672	0.016
Age groups				
18-34	1		1	
35-49	0.796	0.038	0.837	0.135
50-59	0.742	0.015	0.809	0.110
60-64	0.706	0.052	0.710	0.075
>65	0.526	0.001	0.610	0.011
Deprivation category				
1	1		1	
2	0.912	0.672	0.997	0.990
3	0.900	0.612	0.901	0.646
4	0.930	0.721	0.983	0.939
5	0.994	0.977	1.106	0.678
6	1.155	0.518	1.272	0.312
7	0.956	0.861	0.980	0.942
Transplant centre				
Centre 1	1		1	
Centre 2	0.462	<0.001	0.464	<0.001
Centre 3	1.299	0.064	1.309	0.069
Centre 4	0.878	0.354	0.911	0.535
Distance to Tx centre				
< 50 km	1		1	
50 –100 km	1.001	0.993	1.056	0.768
> 100 km	0.995	0.989	1.117	0.745
Year on the waiting list	0.963	0.017	0.961	0.022
Time for first RRT to listing	1.008	0.919	1.066	0.432
Type first dialysis	1.079	0.416	1.062	0.544

Table 4.10 Sociodemographic and comorbidity factors and impact on the speed of access to the renal transplant waiting list – comparison of a basic demographic and comorbidity adjusted models.

In the basic socio-demographic model, primary renal disease and age at listing were significant determinants of access to transplantation ($p = 0.041$ and $p = 0.006$ respectively, Cox regression analysis). After adjustment for the comorbid conditions, both variables lose their impact on the likelihood of transplantation ($p = 0.113$ and $p = 0.87$ respectively, Cox regression analysis), suggesting that their effect could have been due entirely to an unequal comorbidity load for different age groups or causes of renal failure.

Patients over 60 years old maintain a diminished chance of transplantation when compared with patient aged 18-34 years old in both models. However, in the comorbidity adjusted model, all patients under 60 years old have comparable chances of receiving a kidney allograft, irrespective of the donor factors ($p>0.05$, Cox regression).

The only variables with significant impact on the rate of transplantation are the year of listing and the transplant centre. Patients listed in centre 3 have a 30% higher chance of transplantation (RR = 1.30, $p= 0.069$) compared with patients listed in centre 1, while those listed in centre 2 have a 54% lower transplantation rate when compared with the same centre (RR=0.46, $p<0.0001$). All the remaining variables presented in table 5.10 have no significant impact on the rates of transplantation in neither the basic or the comorbidity adjusted models.

Once listed, patients spend on average 634 days (21 months) on the active waiting list until they are transplanted. The comorbidity load exhibited by a particular patient may lengthen this interval by a significant margin. As shown in figure 4.3, the presence of cardiac arrhythmias will double the waiting time for a transplant, while

patients with peripheral vascular disease will spent 26% more time on the waiting list compared with those patients with normal blood vessels. Other cardiac conditions (LVH, valvular disease, ischaemic heart disease) will lengthen the waiting time by 10-20%, while patients with heart failure will be transplanted quicker than those with normal heart function, as a possible indicator of medical urgency and dialysis treatment failure.

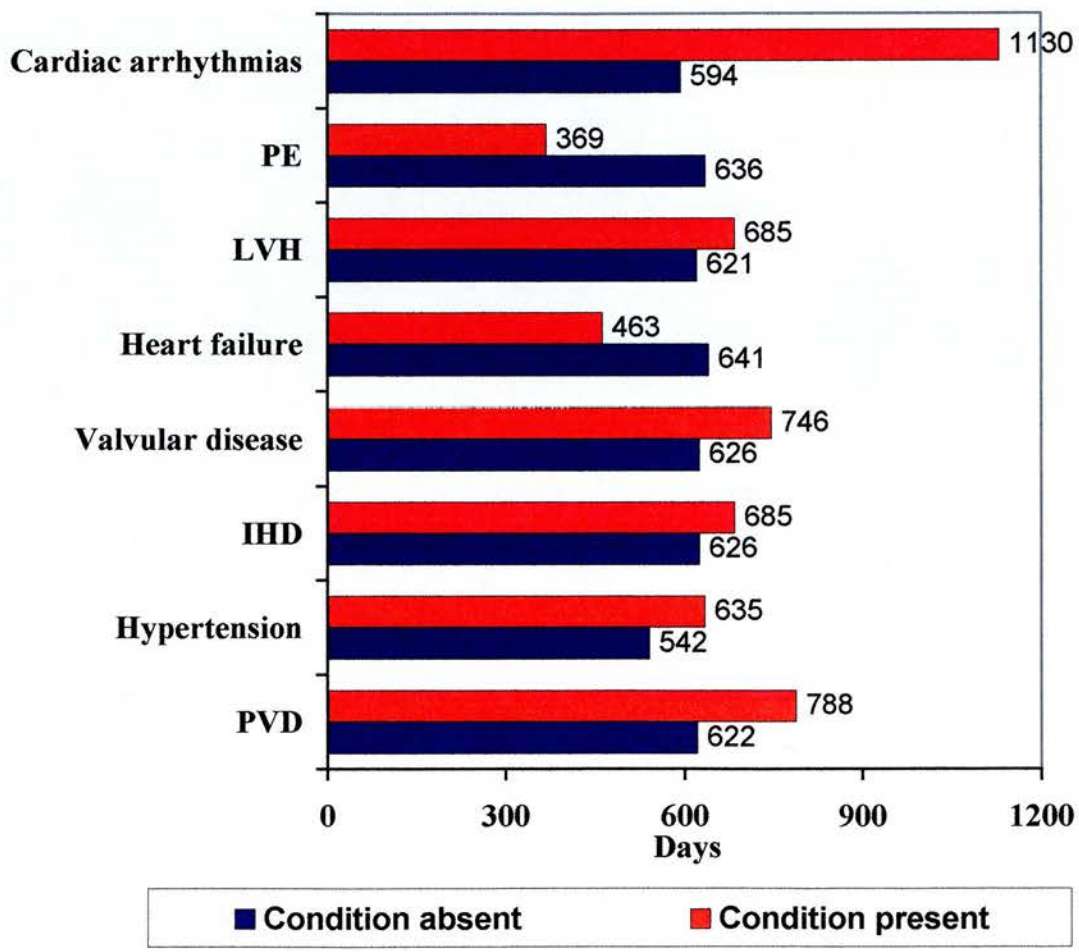


Figure 4.3 Median time of access to transplantation from the listing moment for patients with cardiovascular comorbidity (adjusted for all sociodemographic and comorbid variables)

Patients with diabetes not leading to renal failure tend to be transplanted quicker (table 4.4) and this counterbalances the longer time of access to the waiting list as shown in table 4.2.

A series of other comorbid conditions shown in table 4.4 will prolong the time spent on the active waiting list.

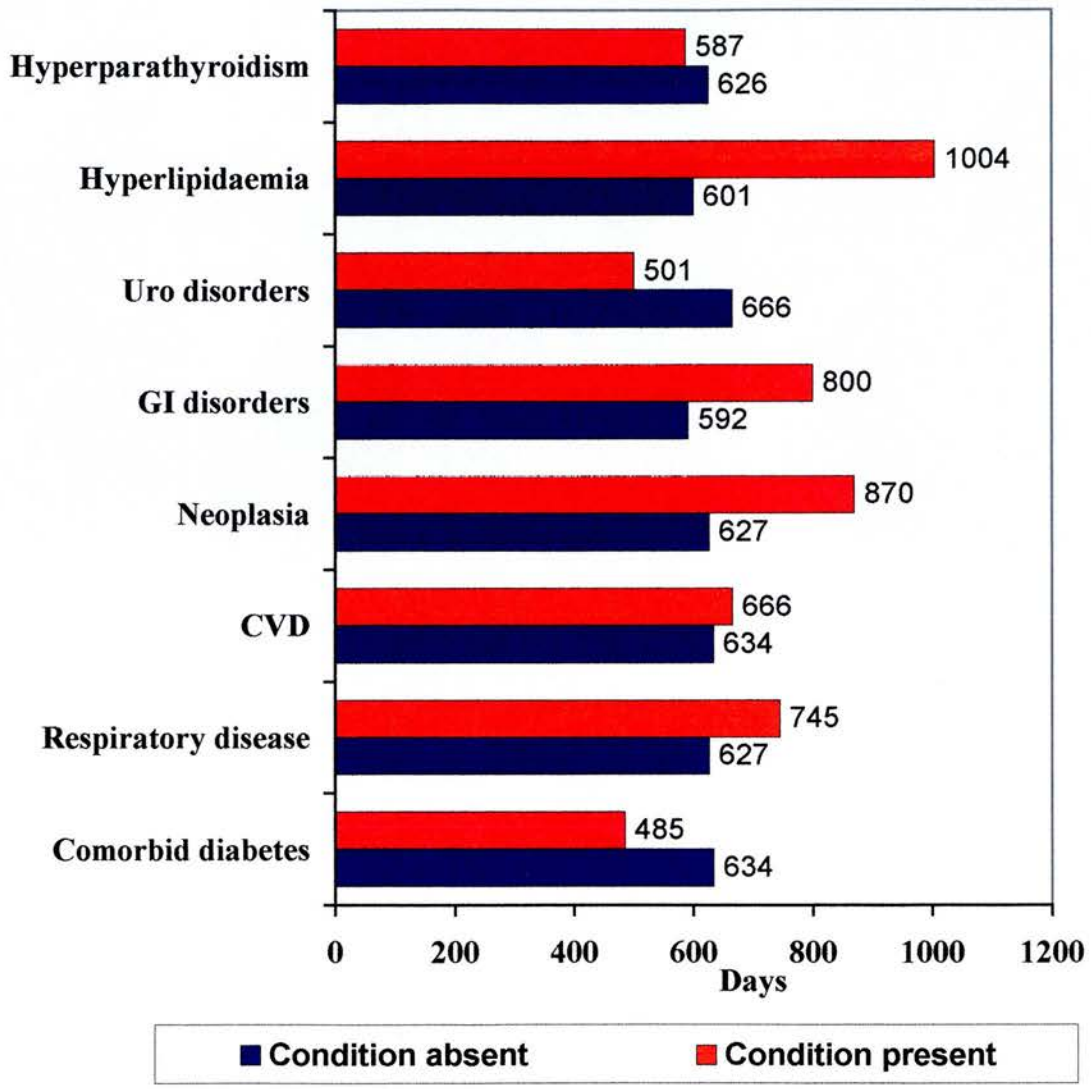


Figure 4.4 Median time of access to transplantation from the listing moment for patients with various comorbid conditions (adjusted for all sociodemographic and comorbid variables).

All these figures should be interpreted bearing in mind that despite a longer waiting time for patients with most of the comorbid conditions, only the presence of cardiac arrhythmias and hyperparathyroidism were found in the multivariate analysis to reduce the transplantation rates by a significant margin.

Suspensions from the active waiting list

Around 26% of the transplanted patients were suspended or removed from the list during the follow-up period. As patients are exposed to the risk of transplantation only when they are on the active waiting list, for all the above analyses, only time spent on the active list was taken into account. However, the amount of time spent off the list during the follow-up period, until receiving a kidney graft, is a good indicator of fitness for transplantation, as patients are usually removed/suspended from the active list for medical reasons. To investigate this issue we compared the difference in the proportion of patients suspended/removed from the active waiting list (figure 4.5) and the median suspension times (figure 4.6) for various categories of patients who received a kidney transplant during the follow-up period (minimum one year).

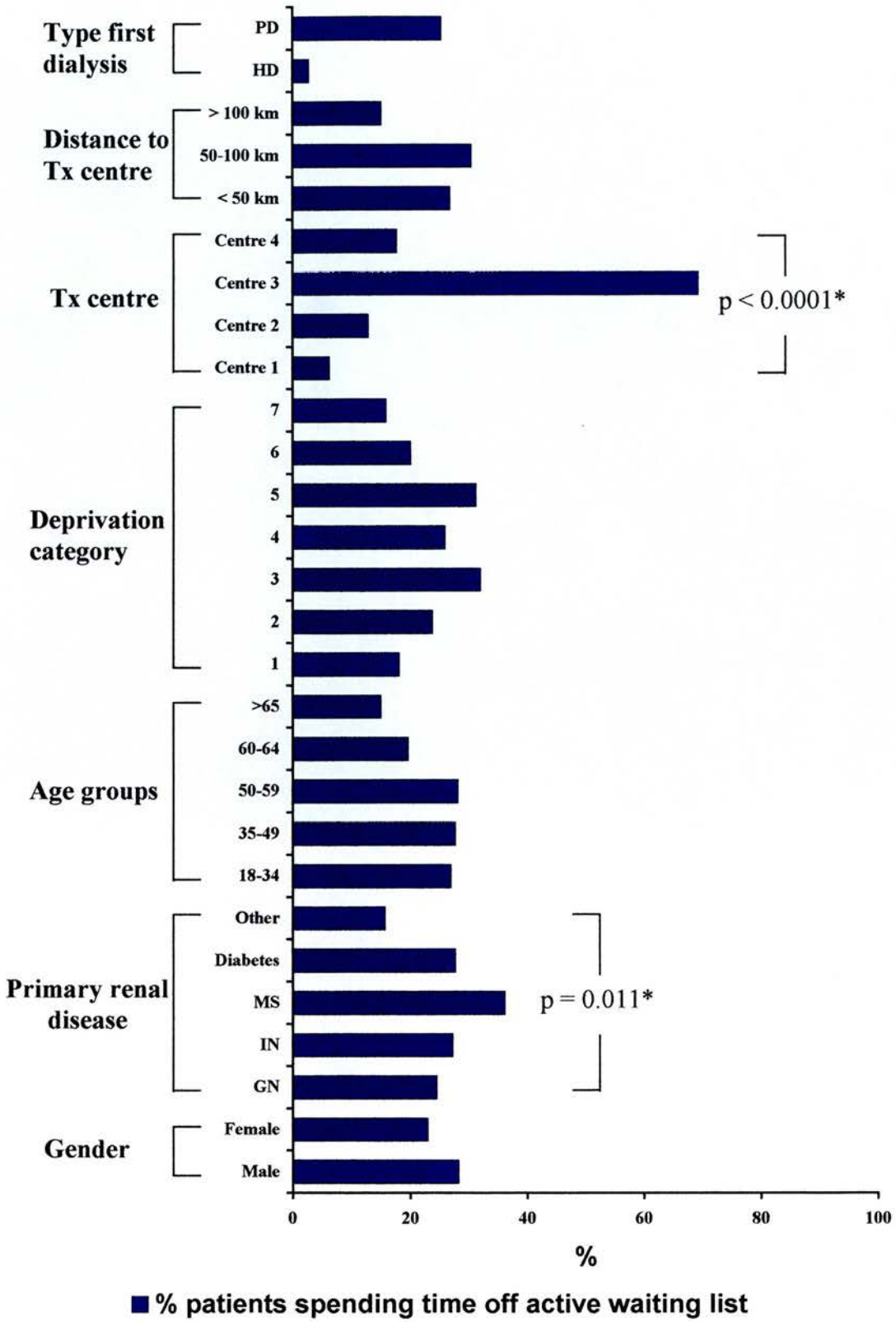


Figure 4.5 Proportion of patients spending time off the active waiting list in different groups of transplant recipients (*, χ^2, $p < 0.05$ statistical significant)

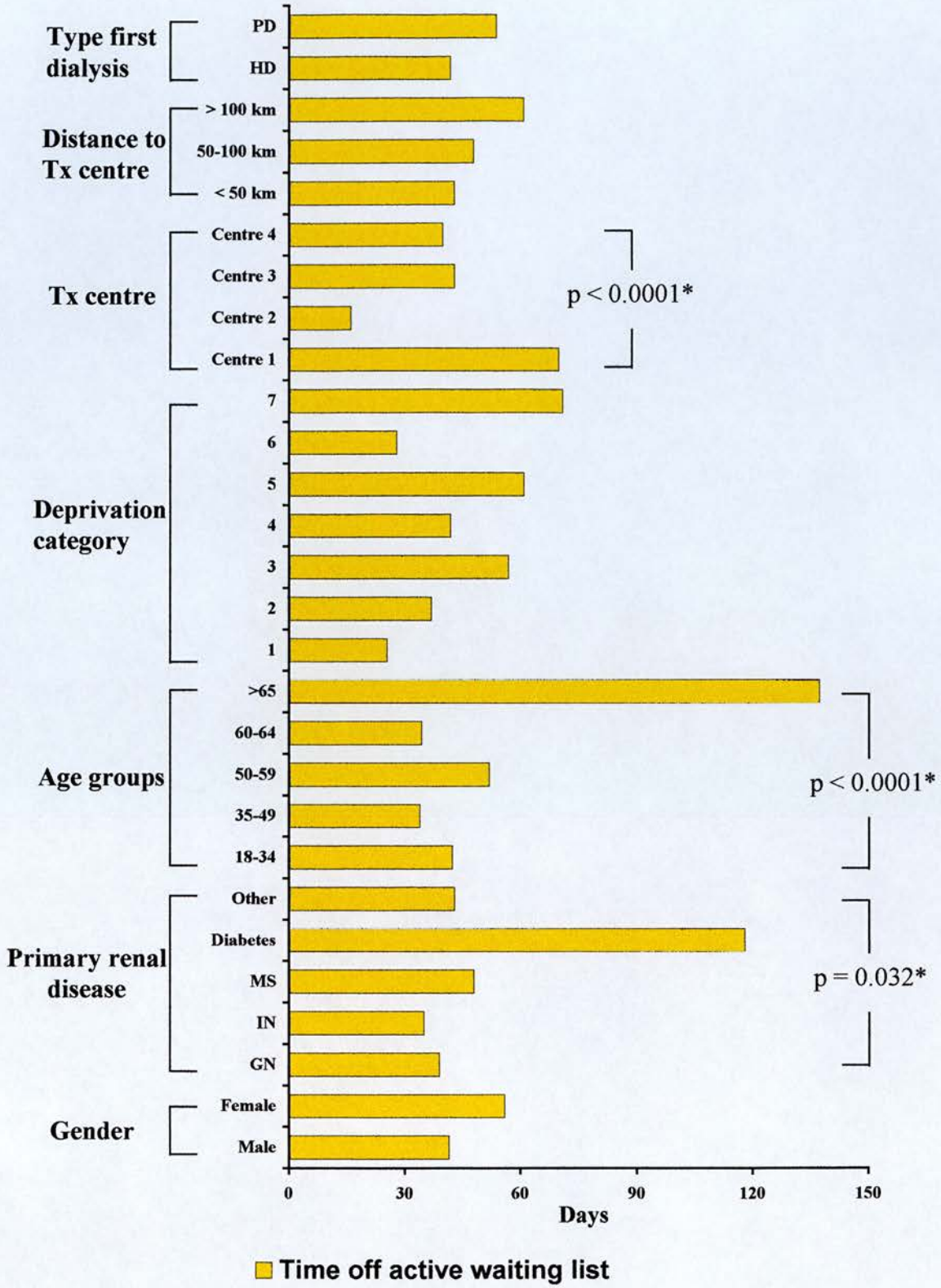


Figure 4.6 Time spent off the active waiting list (days) for different groups of transplant recipients (*, Mann-Whitney U test, $p<0.05$ statistical significant)

When the four transplant centres were compared, significant differences were noticed. Centre 1 has the highest threshold for suspending patients from the list, only 6.3% of the transplant recipients spending time off the active waiting list, but the actual suspension time is by far the longest (median 70 days). Almost 70% of the patients that are eventually transplanted in centre 3 acquire suspensions from the active waiting list. This unusually high proportion may be due a more precise record keeping and patient status tracking to avoid unnecessary shipping of well-matched kidneys for unsuitable recipients.

There are no differences in the proportion of suspended patients according to their age. In fact the elderly group (>65 years old) has the lower proportion of suspensions (15%) but these patients spend the longest time off the active list (median 137 days), almost three times longer than all other transplant recipients.

Significant differences in both the proportion of patients and the length of time off the list are noted according to the primary renal disease. Nearly one third of the diabetic patients spend an average four months suspended or removed from the list prior to receiving a transplant.

Although there are differences in the length of time spent on the active waiting list depending on the associated medical pathology, the presence of any given comorbid condition does not lead to a prolonged length of time spend off the list nor to increased numbers of patients being suspended.

4.4 DISCUSSION

The general health status of a patient is a significant factor in deciding eligibility for the waiting list and renal transplantation. This decision is most frequently governed by previous experience and strong clinical reasons (170;222) rather than being evidence based, as data to support the impact of the associated medical conditions on the likelihood of listing and transplantation (130;131;218) and survival is scarce.

Comorbidity is not collected exhaustively and routinely and some of the difficulties in determining the magnitude of its' impact have been alluded to in the introduction. Although attempts have been made in the US, where the United States Renal Database System (USRDS) and the Health Care Financing Administration (HCFA) collected some core comorbidity data as part of quality-assurance monitoring (220), no further significant developments have taken place. Therefore, there is a need to collect accurate data prospectively, which will allow a systematic and "definitive" analysis of the magnitude of comorbidity effect on access to the transplantation service and survival.

This study presents, in a large sample of adult patients listed for transplantation in Scotland, a systematic, national-level analysis of the relationship between the comorbidity conditions present when patients are listed for transplantation and access to the waiting list and renal transplantation.

There are an important number of comorbid factors that determine how quickly a patient is likely to be listed. Left ventricular hypertrophy, respiratory or cerebro-vascular diseases exert an independent negative effect on the speed of access to the renal waiting list. In addition, marginal effects were noted for patients with diabetes not leading to renal failure, and urological pathology, but the value of this latter finding must be interpreted with care in the absence of a predictive value in the univariate analysis. Interestingly, the presence of hypertension will lead to a shorter time on dialysis pre-listing. If this is interpreted as a marker of an advanced stage of the disease (when hypertension is almost the norm) and inadequacy of the replacement dialysis therapy, one can speculate that patients reaching a certain phase of the disease tend to be referred and accepted for transplantation much quicker than other patients. A few other indicators of cardio-vascular status – ischaemic heart disease, heart failure, valvular disease and peripheral vascular disease - despite a significant association with a longer waiting time in a univariate analysis, did not reach statistical significance in a multivariate Cox model. A few explanations may be possible. First of all, there may be a potential association of these variables with other factors included in the model. Secondly, this analysis was carried out in patients that were eventually listed and hence their true impact on the likelihood of listing could not be assessed. There is no reason to believe that the significant association with lower transplantation rates noted elsewhere (130) will not be seen in Scotland, particularly on a background of increased incidence of cardiovascular morbidity. However, this point cannot be proven by the present study, but the longer waiting time to listing can be used as a surrogate marker of the effect of each comorbid condition.

Although a number of comorbid conditions have a significant impact on the likelihood of transplantation in a univariate analysis (peripheral vascular disease, ischaemic heart disease, cardiac arrhythmias, left ventricular hypertrophy, GI disorders and hyperparathyroidism), only two of them – cardiac arrhythmias and hyperparathyroidism - remain predictive in a multivariate study. It is interesting to note that the number of comorbid condition that influence the chances of listing is much higher than those which will impact on the likelihood of transplantation. This denotes a significant selection process when patients are assessed, few patients with significant associated medical conditions being considered suitable for a kidney transplant in the current practice. In other words, the prevalence of the comorbid conditions is worse among patients on dialysis compared with kidney transplant recipients.

The use of a complex model which controls for the comorbid conditions allows not only to determine the impact of each associated medical condition, but more important, to assess the changes in a basic model containing only socio-demographic variables. When the two models predicting the access to the waiting list were compared, a moderate improvement in the power of the model was noted. However, the level of significance of the individual socio-demographic variables was not diminished by the addition of comorbidity, female patients, elderly patients, diabetics, patients with multisystem disease and patients on haemodialysis waiting longer to be listed.

There are significant changes in the predictive value of the socio-demographic variables when the model of access to transplantation is corrected for comorbidity. In a basic model, patient's age was an independent predictor of access to

transplantation, but after adjustment for comorbidity, the effect becomes non-significant, patients under the age of 60 having similar transplant rates when compared with those aged 18-35 years old. This suggest that age does not have an independent impact on access to transplantation until the age of 60 and that the lower transplantation rates noted for the patients < 60 years old in the basic socio-demographic model are due to a higher prevalence of comorbid conditions in this group. A similar change was noted for the primary renal disease, after adjustment for comorbidity, the differences between various diagnostic groups becoming less prominent. The lower transplantation rates for diabetics compared with glomerulonephritis patients approached statistical significance prior to comorbidity adjustment but were comparable afterwards, implying that diabetic patients have a higher index of associated medical conditions, which is responsible for their lower transplantation rates.

It is not surprising that patients with certain comorbid conditions wait longer prior to listing (figures 4.1 and 4.2) and transplantation (figures 4.3 and 4.4) but it is important to highlight two important issues. First of all, with the current assessment protocols, once a patient is listed, there is very little in terms of significant comorbid illnesses that will preclude someone from becoming a kidney recipient. This is likely to change with the trend towards more elderly and other higher risk patients being put forward for assessment. Therefore a prospective study involving all patients starting RRT may be the answer to address the impact of all these factors on access to transplantation. Secondly, the differences highlighted here indicate that patients who will remain longer on dialysis have a higher prevalence of comorbidity. As previous studies focusing on survival found (as expected) a higher mortality risk

associated with the presence of comorbid conditions (220), it is also important to revisit the question of survival and to compare the benefit of transplantation with that of dialysis in various groups of patients adjusting for the comorbidity load. By doing so, one can estimate the risk of death on either treatment modality and than draw valid, evidence-based criteria for selecting patients onto the waiting list. Furthermore, this will allow patients to make a fully informed choice regarding the best form of treatment, their chances of receiving a kidney transplant and the likelihood of survival according to their general health status.

This study is one of the first of its kind to incorporate the comorbidity load and it provides a more accurate picture of the equity of access to the transplantation service across Scotland. However, the conclusions of this analysis are drawn on 60% of all adult patients listed within the study period and therefore they must be interpreted with care and not extrapolated to the whole population. The retrospective, single-handed collection of comorbidity is far from ideal and may expose the results to bias. Within these limitations, the value of these analyses lies in the fact that for the first time in these sort of investigations a complete picture of the general health of the transplant candidates has been accounted for. In terms of the findings, it is clear that the differences in access to the waiting list and transplantation noted for different socio-demographic variables cannot be explained entirely by the presence of the comorbid conditions.

In summary, the presence of comorbid conditions in a transplant candidate is likely to increase the waiting time by a significant margin, but the number of significant factors may be lower than previously expected. The addition of comorbid conditions to a model of access to renal transplantation improves its' predictive power but

socio-demographic variables (gender, age, primary renal disease, type of first dialysis, deprivation category, transplant centre) remain important indicators of reduced access to the transplantation service.

CHAPTER 5

SURVIVAL ADVANTAGE OF RENAL TRANSPLANTATION COMPARED WITH DIALYSIS

5.1 INTRODUCTION

It is very important to highlight differences in access to the transplantation services as kidney transplantation provides an important treatment option. Improvements in immunosuppressive medication, organ procurement and preservation, patient assessment and selection as well as surgical technique have resulted in graft survival ranging between 80 and 90% after 1 year and 65 to 70% after five years (Table 1.1, Chapter 1). Furthermore, renal transplantation is associated with a superior quality of life and a significant cost-benefit (25;223). Survival on dialysis itself has improved throughout the years due to better therapeutic regimens and patient monitoring. Given the continuing increase in the number of patients requiring renal replacement therapy and the considerable expenses associated with this treatment, it is important to determine the likelihood of survival on both dialysis and transplantation.

Many of the epidemiological studies comparing the outcome of the two treatment modalities in the 80's (224;225) failed to identify a significant survival benefit of transplantation over dialysis and this obviously raised the issue of whether transplantation is beneficial for all patients on dialysis (226). However, most of these studies (138;225;227) were seriously biased for a few reasons. First, comparisons were made between transplant recipients and all chronic dialysis patients. The benefit of transplantation may have been exaggerated by this method, as patient selection is likely to play a significant role, transplant recipients being selected from a group of patients considered fit for transplantation, who are on average, younger and have less

comorbidity (126;130;146). Furthermore, some investigations are not valid as they compare survival from time of transplantation for transplant recipients with survival from the start of RRT for dialysis patients. Thirdly, in these analyses, there is a time-to-treatment bias, as transplantation takes place at a variable interval from listing. This needs to be corrected with a time-dependant analysis (228), which attributes survival before transplantation to the dialysis group. On the other hand, these comparisons were done in the pre-cyclosporine era, when transplant survival was significantly lower than currently attainable.

Recent studies from Michigan (21) and Ontario (229) as well as a national-based US investigation (19) have eliminated these biases, comparing survival in patients who were listed for transplantation and using a "time-to-treatment" approach. A comparison of the crude death rates in these studies (table 5.1) shows that transplantation reduces the chances of dying by about 20-40%.

Study	Patients listed	Crude death rate	Patients Tx	Crude death rate
Michigan	1569	10.7	799	8.6
Ontario	1156	5.0	722	3.4
US study	46164	6.3	23275	3.8

Table 5.1 Crude death rate for listed patients and transplant recipients (death calculated per 100 years of patient follow-up).

An analysis of survival at various time points following a kidney transplant showed that the risk of dying following transplantation is significantly higher in the immediate postoperative period when compared with dialysis. The risk levels out during the first year and becomes significantly lower after this period, as shown in table 5.2.

	Number listed	< 30 days	31-365	>365	18 months
All patients					
Michigan	1569	2.43	0.96	0.36	
Ontario	1156	2.91	0.85	0.25	
US study	46164	2.8			0.32
Diabetes mellitus					
Michigan	483	1.94	0.62	0.25	
Ontario	222	1.87	0.79	0.38	
US study	15187				0.27
GN					
Michigan	369	1.58	2.08	1.16	
Ontario	413	1.55	0.75	0.13	
US study	10156				0.39

Table 5.2 The relative risk of death following transplantation at various time points, compared with dialysis. (The reference group are all patients listed for transplantation on dialysis)

The US based study published by Wolfe et al. (19) uses a more complex statistical analysis, with an exponential decay component which is closer to real life situation and allows the calculation of the number of days between placement on the waiting list and the time when the death rates becomes equal in the two groups.

However, most of the findings reported so far are based on the US experience, where patient selection and access to transplantation are different from most other programmes and therefore, these results cannot be extrapolated to a European setting. Furthermore, survival on dialysis and the 5-year survival on transplantation are significantly lower in the US than in United Kingdom (appendix, table A.2, page 330 and table A.3, page 331) and the rest of Europe (230;231). Although much more limited, there is some data from European single centre analyses (152;232) that confirm the results of the American studies, with a substantial benefit for transplantation compared with dialysis (Relative risk of death of 0.23, 0.34 and 0.31 at 3, 5 and 8 years from listing respectively) (152).

Nevertheless, these studies are small, and there is no large, national experience reported yet. As there are no UK data on this issue, we decided to investigate whether there is indeed a survival advantage for transplantation compared with dialysis in Scotland.

5.2 METHODS

All 1736 adult patients that started dialysis and who were listed for transplantation between 1st of January 1989 and 31st of December 1999 in Scotland were considered for this study. Demographic data for these patients obtained from the Scottish Renal Registry and UK Transplant included: age at listing/transplantation, dates of listing and transplantation, dates of death and last follow-up, gender, primary renal disease, type of first replacement therapy and length of dialysis pre-listing, deprivation score and listing/transplant centre. Extensive data on comorbidity accrued until listing was collected from the case-notes for 1022 patients (59% of all patients listed) (see chapter 4).

Two Cox regression models (unadjusted and adjusted for comorbidity) were built to identify the factors associated with an increased risk of death in the dialysis waitlisted patients and among transplant recipients. Patients who received a transplant were censored at the time of grafting in the dialysis group analysis.

Survival was considered from the time of listing until death, end of study (December 2000) or last follow-up available whichever came first. A time-dependant Cox regression analysis (228), adjusted for the demographic (model 1) and comorbidity variables (model 2), was employed to account for the fact that patients switch between dialysis and transplantation during follow-up. All patients contributed follow up time to the dialysis group, while those receiving a kidney transplant contributed follow-up to the transplant group after grafting (221;233). The effect of transplantation is reported as relative risk (RR) of death, which is the ratio of death

among transplant recipients relative to dialysis patients on the waiting list. The average relative risk of death was estimated for three intervals following transplantation: 0 – 30 days, 31 – 365 days and beyond 365 days and is presented with 95% confidence intervals. The analysis was performed in an intention to treat manner, patients being kept in the analysis, irrespective of subsequent suspensions from the waiting list or graft loss. This type of analysis will estimate the impact of receiving a transplant on survival, irrespective of the subsequent fate of the transplanted kidney. A separate analysis to estimate the impact of a functioning transplant on survival was performed as a comparison, censoring transplant recipients at graft failure (including death with functional graft). In this analysis, after the transplant failed, surviving patients contributed follow-up to the dialysis group.

Survival curves were generated using a Kaplan-Meier method, while differences in proportions and means were tested using χ^2 test and t-test respectively, with a p value ≤ 0.05 considered as significant. The projected years of life on dialysis and with a kidney transplant from the waiting list moment were determined assuming a constant death rate throughout the study period. In the groups which are not followed up until 50% of the patients have died, a continuing death rate equal to the one observed was assumed. Based on individual times of transplantation, the life expectancy was determined for each patient. This allowed the calculation of an average for each subgroup and for the whole study population.

5.3 RESULTS

4532 adult patients started renal replacement therapy between 1st of January 1989 and 31st of December 1999. 1736 patients (38%) were listed and 1095 (24%) received their first kidney transplant by the end of December 2000.

The survival curves for all patients in the analysis according to their treatment modality and irrespective of the "time-to-treatment" variation suggests a substantial benefit of transplantation over patients on dialysis, irrespective of their waiting list status. In addition, there seems to be a significant selection process for access to the waiting list, as patients who are eventually listed have a large survival advantage over patients on dialysis who have no access to the waiting list (Figure 5.1).

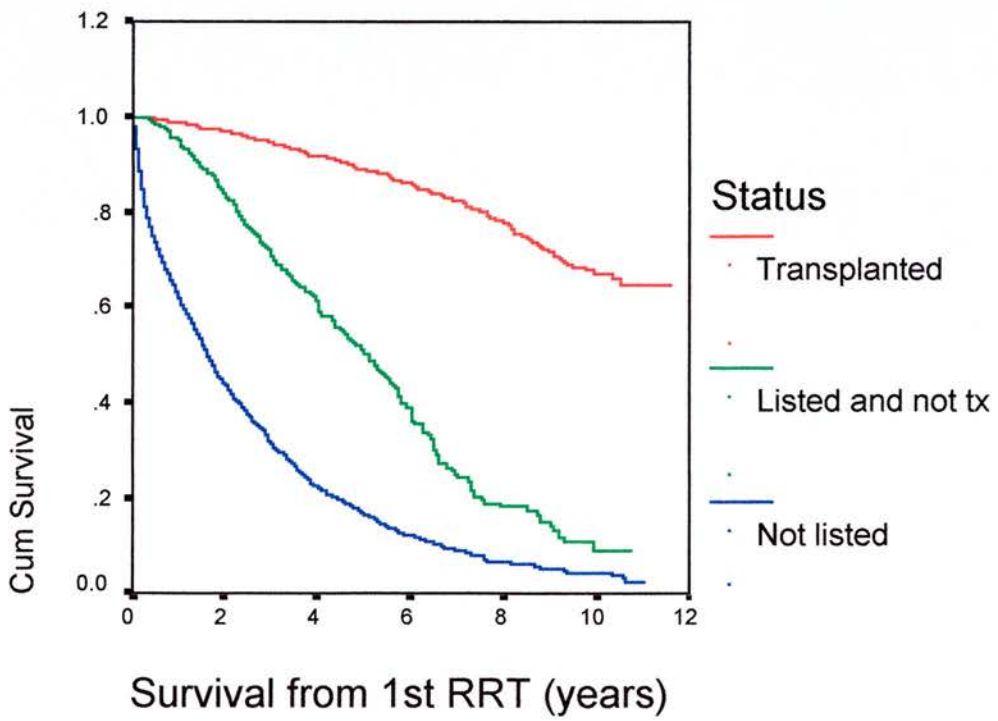


Figure 5.1 Survival curves for all patients starting RRT, according to the treatment status

There is a 63% reduction in the death rates for patients on dialysis who are listed compared with their counterparts who are never listed. Patients who receive a kidney transplant benefit from a further reduction in the mortality rates of 54% compared with listed patients who remain on dialysis (table 5.3).

RRT patients		**Waiting list**		**Tx group**	
Number	Death rate	Number	Death rate	Number	Death rate
4532	24.30	1736	9.02	1095	4.13

Table 5.3 Mortality rates for patients on dialysis, patients listed for transplantation and transplant recipients. (Rate per 100 patient-years of follow-up).

Table 5.4 shows the demographics at the listing moment for all patients and for the two treatment groups (dialysis and transplantation). Although all these patients were considered suitable for transplantation and listed, there are significant differences between the two groups, transplant recipients being listed at a younger age (43 versus 53 years) and sooner after starting renal replacement therapy (0.5 versus 0.78 years). In addition, there is a significantly higher prevalence of diabetes and multisystem diseases as a cause of renal failure in the dialysis group ($p<0.0001$, χ^2) compared with the transplant recipients.

	All listed patients (n=1736)	Listed and on dialysis (n=641)	Listed and transplanted (n=1095)	p value
Age at listing (mean±SD)	46.60±14.14	52.77±12.92	42.98±13.56	<0.0001*‡
Gender (%)				0.799
Male	61.4	61.8	61.2	
Female	38.6	38.2	38.8	
Time from 1st RRT to listing (mean±SD)	0.60±0.91	0.78±1.01	0.49±0.82	<0.0001*‡
Deprivation category (%)				0.545
1	5.4	5.9	5.0	
2	12.6	12.0	12.9	
3	24.3	26.3	23.0	
4	25.7	24.0	26.7	
5	14.3	13.2	15.0	
6	12.1	12.6	11.8	
7	5.7	5.9	5.6	
Primary renal disease (%)				<0.0001*
GN	25.8	20.4	29.0	
IN	30.3	24.0	34.1	
Multisystem	14.7	18.2	12.7	
Diabetes	14.6	19.2	11.9	
Other	14.5	18.2	12.3	
Type of first dialysis (%)				0.393
PD	60.3	61.2	59.8	
HD	39.7	38.8	40.2	

Table 5.4 Demographic characteristics at listing for all patients and for the two treatment groups. (* statistical significant, ‡ Two independent samples T-test, all other χ^2)

A comparison of the comorbidity accrued until listing in the two treatment groups is shown in table 5.5. Patients who remain on dialysis have a higher incidence of cardiovascular problems and peripheral vascular disease. Those on dialysis have twice the incidence of myocardial infarction and angina seen in transplant recipients, while valvular disease, arrhythmias, heart failure and left ventricular hypertrophy are also more common in the non-transplant group. There is a significantly higher prevalence of respiratory disease, cerebrovascular diseases (TIA's, CVA's) and gastrointestinal pathology in the dialysis group. These patients have higher lipid levels and smoke (active or ex-smokers) in higher proportions than those who receive a kidney transplant.

Using a Cox regression analysis unadjusted for comorbidity (table A.16, appendix, page 352 and table A.18, appendix, page 354) the demographic factors with a significant impact on the risk of dying, in both the dialysis and transplant groups, were identified. As shown in table 5.6, there is a significantly higher risk of death for both dialysis patients and transplant recipients with increased age.

	Dialysis group (n=312)	Transplant group (n=702)	p value
PVD	20.2	9.0	<0.0001*
Hypertension	87.5	87.1	0.861
Number of anti-hypertensive drugs (mean±SD)	1.29±1.55	1.20±0.90	0.951‡
IHD	30.8	13.8	<0.0001*
Angina	12.5	5.3	
Myocardial infarction	6.7	2.9	
Valvular disease	17.3	8.7	<0.0001*
PE	1.6	1.4	0.830
Arrhythmias	10.0	3.0	<0.0001*
Heart failure	9.8	5.5	0.013*
Impaired ventricular function	9.7	5.4	<0.0001*
LVH	41.3	29.1	<0.0001*
Respiratory disease	17.2	12.8	0.061
CVD	12.9	8.6	0.035*
Previous neoplasia	2.3	2.1	0.919
GI disorders	29.7	19.4	<0.0001*
Hyperlipidaemia	15.3	8.3	0.002*
Smoker	50.1	41.7	<0.0001*
BMI (mean±SD)	24.73±5.38	24.04±4.87	0.051‡

Table 5.5 Comorbidity prevalence in the two treatment groups at listing (* statistical significant, ‡ Two independent samples T-test, all other χ^2)

Covariate	Dialysis patients on the waiting list RR (95%CI)	p value	Transplant patients RR (95%CI)	p value
Gender				
female vs. male	0.913 (0.713-1.171)	0.475	0.973 (0.705-1.343)	0.868
Renal disease		<0.0001*		<0.0001*
GN	1		1	
IN	0.776 (0.515-1.169)		0.945 (0.620-1.441)	
MS	1.139 (0.750-1.732)		1.081 (0.666-1.756)	
Diabetes	3.454 (2.399-4.973)		2.642 (1.705-4.091)	
Other	1.352 (0.903-2.024)		1.139 (0.663-1.956)	
Type of 1st RRT				
HD vs PD	1.176 (0.913-1.514)	0.210	1.424 (1.049-1.932)	0.023*
Age at listing		<0.0001*		<0.0001*
18-34	1		1	
35-49	2.743 (1.579-4.767)		2.303 (1.353-3.919)	
50-59	4.518 (2.648-7.710)		4.573 (2.728-7.666)	
60-64	5.500 (3.069-9.854)		8.172 (4.513-14.797)	
>65	7.588 (4.355-13.221)		8.679 (4.779-15.761)	
Time to listing *per year*	1.355 (1.189-1.544)	<0.0001*	1.074 (0.880-1.311)	0.485
Time from waiting list to Tx *per year*	-	-	1.000 (0.999-1.000)	0.436

Table 5.6 Risk of death by demographic factors in the dialysis group and after transplantation (unadjusted for comorbidity). (*, Statistical significant)

Diabetes as a cause of renal failure leads to the highest risk of dying on the waiting list, as well as after transplantation, when compared with glomerulonephritis patients [RR=3.454, 95%CI: 2.399-4.973 and RR=2.642, 95%CI: 1.705-4.091 respectively]. The time elapsed between the start of RRT and listing is a significant predictor of death for dialysis patients but not for the transplant recipients. Every increase of one

year in the length of time on dialysis prior to listing is associated with an increase in the risk of dying on the waiting list of 1.355 (95%CI 1.19-1.54). The time spent on the waiting list before receiving a kidney allograft has no impact on the risk of dying after transplantation. Interestingly, patients who start RRT on haemodialysis have a higher risk of death compared with those on peritoneal dialysis if they receive a kidney transplant, but not if they remain on dialysis on the waiting list.

When comorbidity conditions are taken into account (table A.17, appendix, page 353 and table A.19, appendix, page 355), all the variables identified in the previous models remain predictors of a higher risk of death. As shown in table 5.7, the presence of ischaemic heart disease, respiratory and cerebrovascular diseases in a transplant candidate is associated with an increased risk of death on dialysis, while previous neoplasia and gastrointestinal pathology are associated with a higher risk of dying following transplantation.

Covariate	**Dialysis patients on the waiting list**	**p value**	**Transplant patients**	**p value**
IHD	1.864 (1.163-2.988)	0.010*	0.863 (0.450-1.656)	0.658
Valvular disease	1.960 (0.911-3.025)	0.018*	1.334 (0.606-2.933)	0.474
Respiratory disease	2.197 (1.341-3.600)	0.002*	1.070 (0.521-2.200)	0.853
CVD	2.455 (1.430-4.215)	0.001*	1.792 (0.782-4.111)	0.168
Neoplasia	2.564 (0.692-9.507)	0.159	3.005 (1.008-8.962)	0.048*
GI disorders	1.336 (0.861-2.074)	0.196	1.771 (1.022-3.067)	0.042*

Table 5.7 Comorbidity factors associated with an increased risk of death on dialysis and after transplantation (adjusted for demographic variables). (*, Statistical significant)

The relative risk of death for transplant recipients compared with patients on the waiting list varies depending on the length of follow-up. The average risk (95%CI) was determined for three periods following kidney transplantation: 0-30 days, 31-365 days and beyond 365 days and is shown in table 5.8.

All patients	*< 30 days*	*31 – 365 days*	*> 365 days*
No comorbidity adjustment	1.35 (0.63-2.86)	0.67 (0.48-0.95)	0.32 (0.25-0.40)
Comorbidity adjusted	0.91 (0.22-3.70)	0.50 (0.28-0.90)	0.28 (0.20-0.39)

Table 5.8 Relative risk of mortality over time after transplantation versus dialysis patients on the waiting list. (Non-proportional Cox models adjusted for age, gender, primary renal disease, social deprivation, time since waitlisting [model 1] and comorbidity [model 2])

When compared with patients on the waiting list, transplant recipients appear to have an increased risk (although not statistically significant) of death within the first month following grafting (RR=1.35, 95%CI: 0.63-2.86). The risk becomes lower during the first year post transplant and is significantly reduced beyond one year. The long-term mortality risk for transplant recipients is 68% lower than that of patients on the waiting list (RR=0.32; 95%CI: 0.25-0.40; $p<0.0001$). The same evolution of the risk of death was noted when the model was adjusted for comorbidity factors (table 5.8).

The outcome varies among different subgroups of kidney transplant recipients, as shown in table 5.9.

Subgroup	< 30 days	31 – 365 days	> 365 days
Gender			
Male	1.51 (0.37-6.28)	0.55 (0.26-1.17)	0.29 (0.18-0.45)
Female	-	0.50 (0.20-1.29)	0.32 (0.18-0.59)
Primary renal disease			
GN	-	0.38 (0.08-1.72)	0.16 (0.07-0.39)
IN	-	1.09 (0.39-3.04)	0.28 (0.13-0.61)
Multisystem disease	1.82 (0.22-14.80)	0.48 (0.13-1.77)	0.13 (0.04-0.38)
Diabetes	1.28 (0.17-9.83)	0.40 (0.12-1.36)	0.33 (0.15-0.74)
Other	-	-	0.11 (0.02-0.70)
Age groups			
18-34	-	-	0.23 (0.05-1.14)
35-49	-	0.64 (0.25-1.61)	0.26 (0.11-0.57)
50-59	1.44 (0.19-11.19)	0.37 (0.11-1.26)	0.12 (0.05-0.27)
60-64	-	0.30 (0.03-2.81)	0.19 (0.04-0.98)
>65	2.38 (0.27-20.84)	0.81 (0.23-2.91)	0.34 (0.14-0.83)

Table 5.9 Relative risk of mortality over time after transplantation versus dialysis patients on the waiting list in different sub-groups of patients. (Non-proportional Cox models adjusted for age, gender, primary renal disease, social deprivation, time since waitlisting, comorbidity) (- ; risk could not be calculated due to too few deaths)

In all groups where the risk could be calculated, there seems to be a higher probability of dying in the immediate post-transplant period. The risk becomes equal during the first year and is significant lower beyond one year in most patients receiving a kidney transplant compared with patients on dialysis, with the exception of patients aged 18-34 years old for whom the benefit of transplantation is not significant even at this time point (RR=0.23; 95%CI, 0.05-1.14; p=0.07).

Diabetic patients have a 67% lower risk of dying at one year after transplantation compared with patients on dialysis (RR=0.33; 95%CI, 0.15-0.74). Although the

initial (<30 days) excess risk was small and not statistically significant, the long term benefit is inferior to that observed in patients with multisystem disease or glomerulonephritis who have an 87% and 84% lower risk of dying one year after grafting. However, statistical comparisons between groups according to the primary renal disease were not appropriate, as the reference group was different for each cause (patients on the waiting list with the respective diagnosis).

There is a significant death risk reduction following transplantation in all age groups. The greatest benefit is achieved in patients aged 50 – 59 years old, while patients aged 18-34 years old see no significant benefit from being transplanted even at one year after grafting.

When survival after transplant is censored for graft failure, the impact of a functioning transplant on survival is determined. As shown in table 5.10, similar results as the ones described so far are obtained. The immediate post-transplant risk of death is significantly higher compared with dialysis and it evens out during the first year. At 12 months, a functioning graft increases a patient's chances of being alive by 70% compared to dialysis.

All patients	*< 30 days*	*31 – 365 days*	*> 365 days*
No comorbidity adjustment	4.69 (3.06-7.17)	0.82 (0.60-1.14)	0.31 (0.24-0.39)
Comorbidity adjusted	3.22 (1.48-6.98)	0.69 (0.41-1.15)	0.30 (0.21-0.43)

Table 5.10 Relative risk of mortality over time with a functioning transplant compared to dialysis patients on the waiting list. (Non-proportional Cox models adjusted for age, gender, primary renal disease, social deprivation, time since waitlisting [model 1] and comorbidity [model 2])

The projected life span was 5.84 years for patients remaining on dialysis and 17 years for the transplant recipients. The differences in the projected life expectancy between transplant recipients and dialysis patients are shown in table 5.11. There is a comparable increase in life expectancy for both genders. Although diabetic patients seem to have the shortest life span, in fact transplantation in these patients leads to the highest proportional increase in the life expectancy compared with other causes of renal failure. In patients aged $\geq$ 65 years old, transplantation leads to a twice longer life expectancy compared with dialysis, this proportional increase being greater than that noted in patients aged 18-34 years old.

	Years of life on dialysis	**Years of life with a kidney transplant**
All patients	5.84	17.19
Gender		
Male	5.63	16.13
Female	5.99	16.98
Primary renal disease		
GN	6.37	17.40
IN	8.90	21.31
Multisystem disease	5.39	14.16
Diabetes	2.92	8.60
Other	5.36	12.27
Age groups		
18 - 34 yr	27.22	41.50
35 - 49 yr	6.71	18.03
50 - 59 yr	5.12	11.18
60 - 64 yr	4.32	7.84
$\geq$ 65 yr	3.69	7.60

Table 5.11 Projected years of life for patients on dialysis and transplant recipients, from the moment of listing for transplantation

5.4 DISCUSSION

The long term survival and risk of death are two of the main indicators for the success of any medical procedure. Since the early days, the outcome of renal transplantation has been compared with that of various dialysis methods. Most of these studies however, were biased by the lack of accurate statistical methods (234). Recent studies, which have eliminated the different biases, described earlier in this chapter, have proven that transplantation provides a significant survival advantage when compared with dialysis (19;21;229), however, data on comorbidity in these studies are limited. Such comparisons based on UK data were not available until now.

In Scotland, there is a significant selection process in listing patients for transplantation. This is illustrated by a 60% reduction in the crude mortality rates for those listed. Furthermore, patients who have access to transplantation, enjoy a further reduction in the mortality risk of about 54%. These results are similar with those reported by Wolfe et al. (19) and other researchers (229) and therefore any survival comparisons between the two treatment modalities should be carried out only in listed patients, to eliminate the selection process.

Although all patients in this analysis were considered suitable for transplantation, there are significant differences between the two groups. Transplant recipients are listed at a younger age and spend a shorter time on dialysis pre-listing than those who remain on the waiting list. Also, fewer diabetics and patients with multisystem disease were transplanted during the follow-up period. As this study covers an 11

year period, these findings seem to suggest significant variations in the selection process as well as a trend to include an increasing number of high-risk patients in the transplantation programme more recently (229;235). A comparison of the comorbidity load confirms this hypothesis, patients who are listed and on dialysis having more comorbid conditions such as peripheral vascular disease, cardio-vascular, respiratory or cerebrovascular problems (table 5.5), which may preclude them from receiving a transplant. Furthermore, some of the demographic variables (age, primary renal disease, time to listing) and comorbid conditions (table 5.7) have an impact on survival on both treatment modalities and therefore any survival analysis must be adjusted for these factors.

The recipients of a kidney transplant have a 68% lower long term (> 1 year) risk of dying compared with dialysis patients on the waiting list after adjustment for age, gender, primary renal disease, length of time on dialysis. Similar reductions in the mortality risk (64 to 75%) were reported in the US (19), Canada (229), Germany (152) and Sweden (232). International comparisons are difficult, due to differences in survival on dialysis (230;231) and transplantation between North America and Europe, but despite the absolute differences in crude mortality rates, the results of these similarly constructed and conducted studies indicate that the effect of transplantation on survival is comparable across the western world.

As comorbidity accrued by patients until the listing moment has a significant impact on the chances of transplantation and survival, we conducted a second analysis on 60% of the listed population for whom these data were available. Significantly more high-risk patients remain on dialysis on the waiting list rather than receiving a transplant, but even after adjustment for comorbid conditions as well as other

demographic variables, transplantation has a persistent survival advantage at one year (RR=0.28, 95%CI: 0.20-0.39) compared with dialysis. Although these results cannot be extrapolated to the whole study population, they are a powerful indicator that transplantation effect is real and it is not induced by selection of healthier patients.

The effect of transplantation on survival varies with time. In the immediate postoperative period, there seems to be an increased risk of death for transplant recipients (RR=1.35, 95%CI: 0.63-2.86). Although these findings did not reach statistical significance, they are in agreement with other published data, suggesting that there is an increased risk of death in the immediate postoperative period. The lack of statistical significance may be explained by an improved postoperative care - which leads to fewer postoperative deaths, and a more strict selection of patients for transplantation in the UK. This seems to be confirmed in the comorbidity adjusted model, where the risk of dying following transplantation is lower than the risk of death on dialysis at all time points.

The magnitude of transplantation survival benefit is not equal for all patients, as shown in table 5.9 and previously reported (19;21;23;236). The risks of death on either transplantation or dialysis are not significantly different in the first postoperative year. Beyond a year, all patients have a better survival with a transplant, irrespective of their primary renal disease. However, patients with diabetes have an inferior long-term benefit when compared with glomerulonephritis patients. This may be due to the fact that diabetic patients represent a high-risk group, which is illustrated by the low proportion of transplants in diabetics (11% vs. 29% with glomerulonephritis). These findings are in contrast with previous reports

from the US (21;143), where over 30% of the transplants take place in diabetic recipients and the survival advantage following transplantation is greater than that attained in glomerulonephritis patients.

Age has a significant impact on the long-term survival chances of a patient, irrespective of the treatment modality. These data indicate that in Scotland, the greatest survival gain associated with transplantation is obtained in patients aged 50-59 years old (RR=0.12, 95%CI: 0.05-0.27). But, perhaps more important, is the fact that patients aged 60-64 years old enjoy a benefit from being transplanted of similar magnitude as patients aged 18-34 years old, in whom, even at one year, survival on dialysis is not significantly inferior to transplantation.

Diabetes is acknowledged as a powerful predictor of death among dialysis patients (236;237) but as shown here and in most studies quoted before (19;21;229), these patients do benefit from renal transplantation. If one compares the survival benefit in diabetics (RR=0.33) with that obtained in patients over 65 years old (who are usually considered to be medically high risk) (RR= 0.34) it is difficult to advocate why transplantation should not be offered to these patients, and indeed other patients considered high-risk, currently not transplanted.

The overall projected increase in the life expectancy with transplantation is 12 years, with variation between 3.5 and 14 years for different groups of patients. Similar benefits have been previously reported in only one large study from the USA (19). These results should be interpreted with caution for several reasons. First of all, they represent extrapolations and therefore the larger estimates may not be accurate. Secondly, this study covers an 11 years period, and during this time there have been improvements in survival for all patients, irrespective of their treatment modality.

Therefore, for some groups of patients, these particular findings may not be predictive.

This study uses an intention to treat analysis, whereby patients are considered to be on the waiting list irrespective of subsequent periods of suspension or permanent removal. Furthermore transplant recipients contributed for the survival on transplantation, irrespective of whether they lost their grafts during the follow-up and returned to dialysis. This has the potential to bias the results in favour of transplantation. There is evidence, from a smaller single-centre study (152), where both an intention to treat analysis as well as an analysis censoring patients at removal from the waiting list or loss of transplant function were performed, that transplantation does provide a significant survival benefit compared with dialysis. On the other hand, most patients are removed from the waiting list due to deterioration in general health and they are likely to die soon after. This has the potential of rendering the death rate on the waiting list almost zero, which would make further comparisons biased as well. In the current analysis it was impossible to identify with certainty the reasons why patients were removed from the waiting list and hence an intention-to-treat design was used. However, it was possible to determine when the graft failed, and therefore a second analysis, censored for graft failure was carried out. This analysis estimated the impact on survival of having a functioning graft and confirmed that immediately after transplantation there is an increased risk of death, but 12 months after a kidney graft, there is a substantial survival benefit over dialysis.

In summary, this study provides evidence that in the current setting of end stage renal failure care in Scotland, there is a substantial long-term survival advantage for

transplantation compared with dialysis. This effect is intrinsic to the treatment itself, rather than an effect of patient selection or higher dialysis mortality. As expected, the survival advantage is not equal across all patients groups, but even high-risk patients enjoy a substantial benefit from being transplanted. This should prompt us to re-consider selection and assessment for transplantation and perhaps a risk assessment score rather than simple criteria such as old age or certain comorbidity should be used to admit patients to the waiting list. In addition, these findings provide a powerful clinical tool, which should be used when advising patients regarding the suitability of dialysis or transplantation as treatment for their end stage renal disease. In a wider perspective, in the current climate of organ shortage, emphasizing the life saving benefit of renal transplantation to the public may have a positive effect on organ donation rates and thus provide the best treatment for larger numbers of patients.

CHAPTER 6

ASSESSMENT FOR RENAL TRANSPLANTATION AND HIGH RISK PATIENTS

6.1 INTRODUCTION

Assessment for listing is the most important step in the pathway to transplantation where someone may be denied further access to the service. There are no uniform criteria for listing, and practices vary widely (199;238). These differences may lead to serious bias against various groups of patients, depending on the transplant centre where they are referred for assessment. Recently, guidelines for assessment and listing were published by the American Transplant Society and suggested by the European Dialysis Association. Most of these guidelines are evidence based and are likely to minimise some of the differences noted previously.

There are no such guidelines in UK, and although the practice is pretty much uniform, there are significant centre variations.

This study aims to present the current status in assessment for listing in Scotland and to highlight whether there are any major differences in assessment between the transplant centres as well as investigating the outcome of transplanting some high risk patients.

To address these issues, a series of separate analyses investigating the differences in practice across Scotland as well as the benefit of transplantation in high risk groups of patients (elderly patients and diabetic recipients) were carried out.

6.2 Patient assessment - current status

6.2.1 Methods

All 1736 adult patients listed for transplantation within the study period (1st of January 1989 – 31st of December 1999) were considered for these analyses. As shown in the previous chapters, sociodemographic data from the SRR and UKT was collated for all patients and in addition, more than 40 comorbidity variables (appendix, page 348-351) were gathered for 59% of the patients on the list (n=1022).

A comparison of the distribution of sociodemographic (age, gender, deprivation category, primary renal disease, type of first dialysis method) and comorbidity variables (diabetes, peripheral vascular disease, cardio-respiratory diseases, cerebro-vascular problems and other detailed in the appendix) across the waiting list population and between the four transplant units was carried out to identify the groups of patients where differences in practice are most obvious.

Chi-square, Fisher's exact test, t-test and Mann-Whitney U tests were used where appropriate, to determine the statistical significance of the differences observed.

6.2.2 Results

The distribution of the socio-demographic variables across the waiting list population has been discussed in chapter 3. The summary shown in table 6.2.1 highlights that there are significant differences, with female patients, elderly patients, diabetics and more deprived patients being less likely to be listed for transplantation.

There is a significant centre effect and these differences may reflect a sociodemographic disparity between the patients seen in each centre, as well as a different clinical view to who actually represents a suitable candidate for transplantation.

A comparison of the proportions of patients listed by gender (figure 6.2.1) revealed significant differences, nearly 54% of all males starting dialysis in centre 1 being listed compared with only 37% of those starting RRT in centre 4. A similar disproportion (50% versus 33%) was noted for females between the same centres.

		RRT population	WL population
Gender	Male	58.5	61.4
	Female	41.5	38.6
Age groups	18-34	12.0	25.7
	35-49	17.3	32.0
	50-59	17.7	24.3
	60-64	13.2	9.0
	>65	39.9	9.0
Deprivation category	1	5.1	5.4
	2	12.7	12.6
	3	21.8	24.3
	4	25.2	25.7
	5	15.1	14.3
	6	12.6	12.1
	7	7.5	5.7
Primary renal disease	Primary GN	16.8	25.8
	Interstitial nephritis	21.7	30.3
	Multisystem disease	23.3	14.7
	Diabetes	16.2	14.6
	Other/unknown	22.0	14.5
Type of first dialysis	Haemodialysis	70.2	60.3
	Peritoneal dialysis	29.8	39.7
Renal unit (1st RRT)	1	9.3	12.8
	2	10.8	13.1
	3	16.3	19.1
	4	20.8	18.1
	5	14.2	13.0
	6	5.5	3.9
	7	3.5	2.6
	8	3.0	1.9
	9	5.4	4.6
	10	3.7	4.1
	11	7.7	6.9
Renal unit in same hospital with Tx centre	Yes	58.3	63.1
	No	41.7	36.9
Listing transplant centre	Centre 1	12.6	16.4
	Centre 2	10.0	11.6
	Centre 3	20.8	21.8
	Centre 4	56.6	50.2
Distance to listing centre	<50 km	85.6	84.8
	50 – 100 km	7.2	7.9
	>100 km	7.2	7.3

Table 6.2.1 Sociodemographic distribution of the dialysis and waiting list populations (% patients in each category in the two populations).

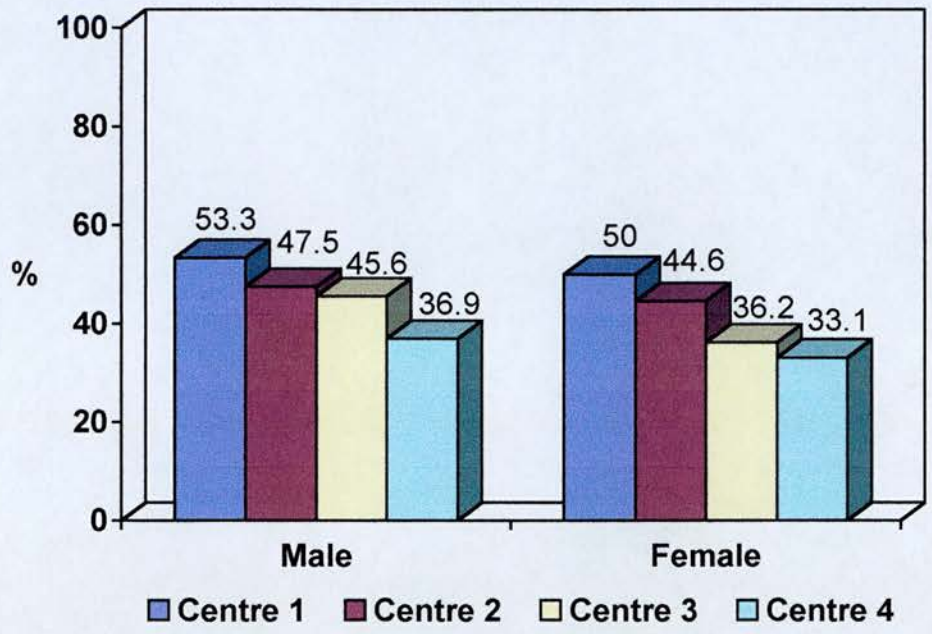


Figure 6.2.1 Proportion of patients listed for transplantation from the total starting dialysis in each centre, according to gender

There are significant differences in the proportions of patients listed in each of the four centres according to the primary renal disease. While for some of the causes of renal failure (glomerulonephritis, interstitial nephritis or other causes) the differences between centres are in the range of 10-15%, the largest disproportion is noted for diabetic patients. Nearly 50% of the diabetics starting RRT in centres 1 and 2 are listed compared with only 38% and 29% respectively in centres 3 and 4.

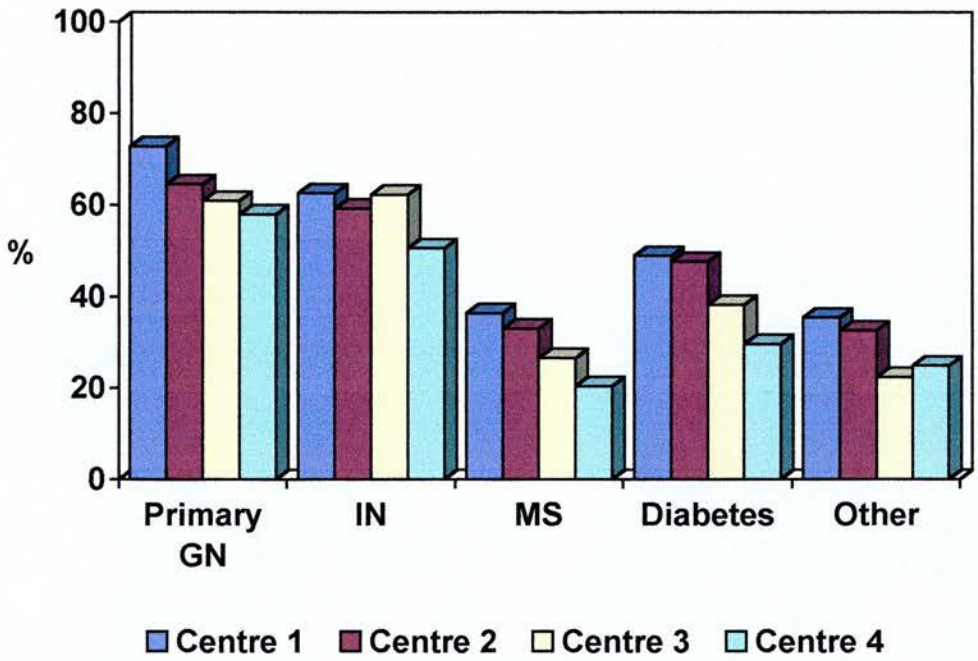


Figure 6.2.2 Proportion of patients listed for transplantation from the total starting dialysis in each centre, according to the primary renal disease (IN = interstitial nephritis, MS = multisystem disease)

Even more striking differences were noted according to patient's age. There seem to be a uniform approach in all centres for listing young (18-34 years old) patients - more than 80% listing rates - but the older the patient, the larger the differences. It appears that patients over 60 years old starting dialysis in centres 1 and 2 have a better chance of being listed compared with those starting RRT in the remaining two centres. Although the overall number of patients starting RRT is much higher in centres 3 and 4 (table 6.2.1), these differences cannot be explained only by the workload and a longer time to assess the potential candidates.

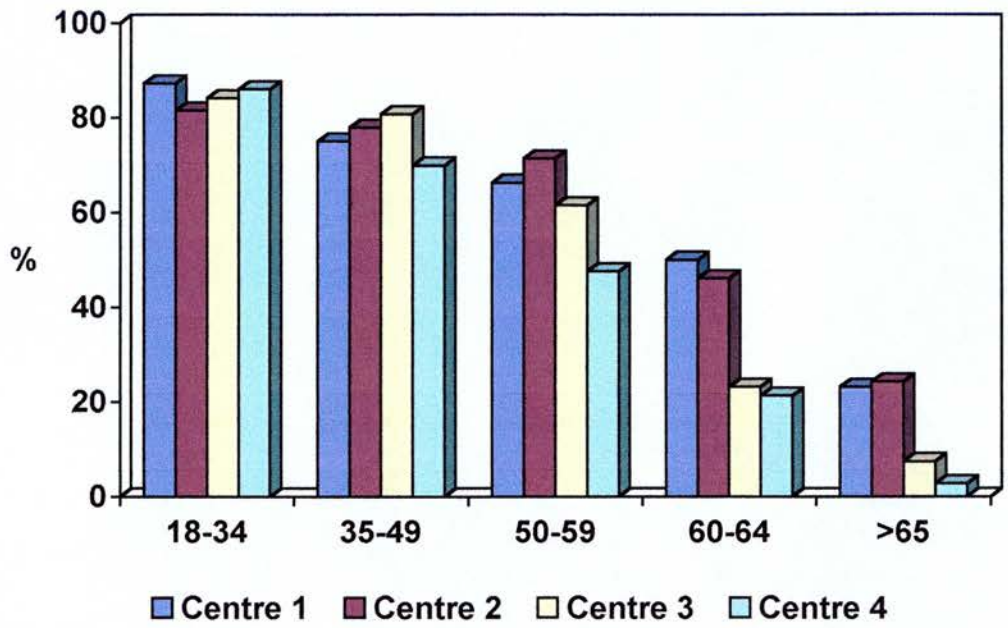


Figure 6.2.3 Proportion of patients listed for transplantation from the total starting dialysis in each centre, according to age at the start of RRT

It can be argued that more patients over 60 years old in centres 3 and 4 may be unfit to be listed and hence the discrepancies between the proportions listed in each centre. However, when the age distribution for the patients that were eventually listed in each centre was compared (figure 6.2.4), these differences persisted. This clearly indicates that there are different approaches to the age criteria in each transplant centre.

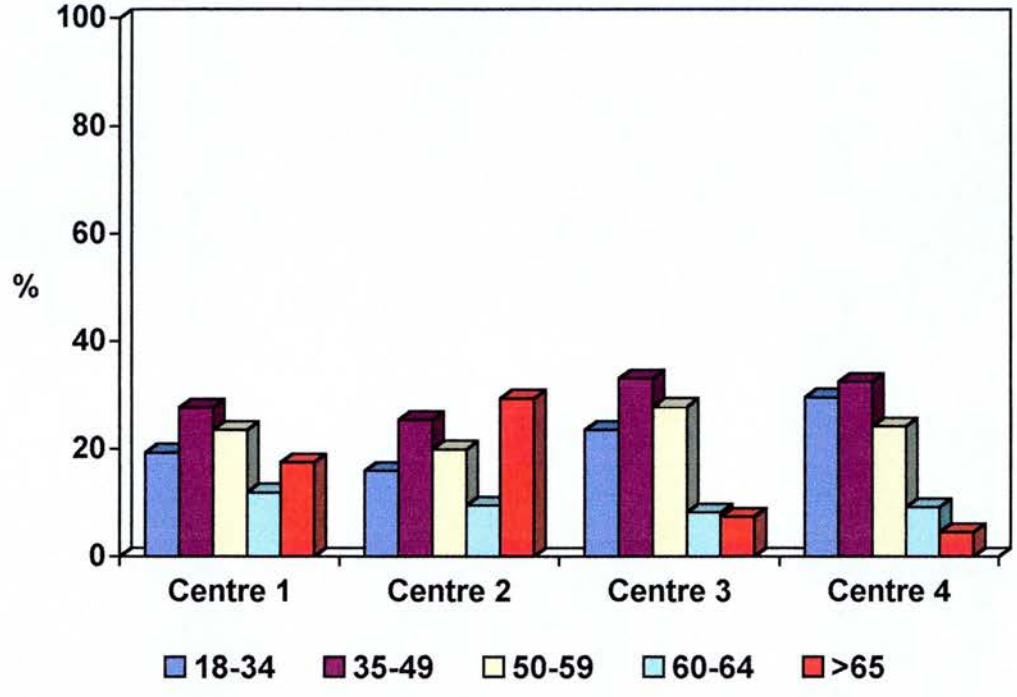


Figure 6.2.4 Age distribution for patients listed for transplantation in each centre.

Centre variations were also noted in the proportion of patients listed according to the type of first dialysis regimen (figure 6.2.5), deprivation category (figure 6.2.6) and distance from patient's home to the transplant centre (figure 6.2.7).

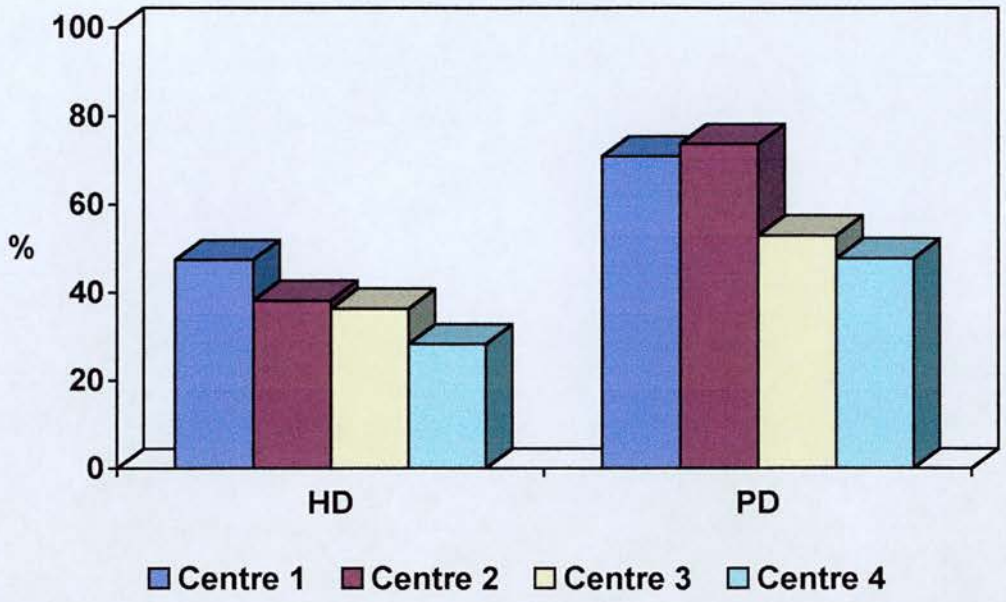


Figure 6.2.5 Proportion of patients listed for transplantation from the total starting dialysis in each centre, according to the type of first RRT (HD = haemodialysis, PD = peritoneal dialysis)

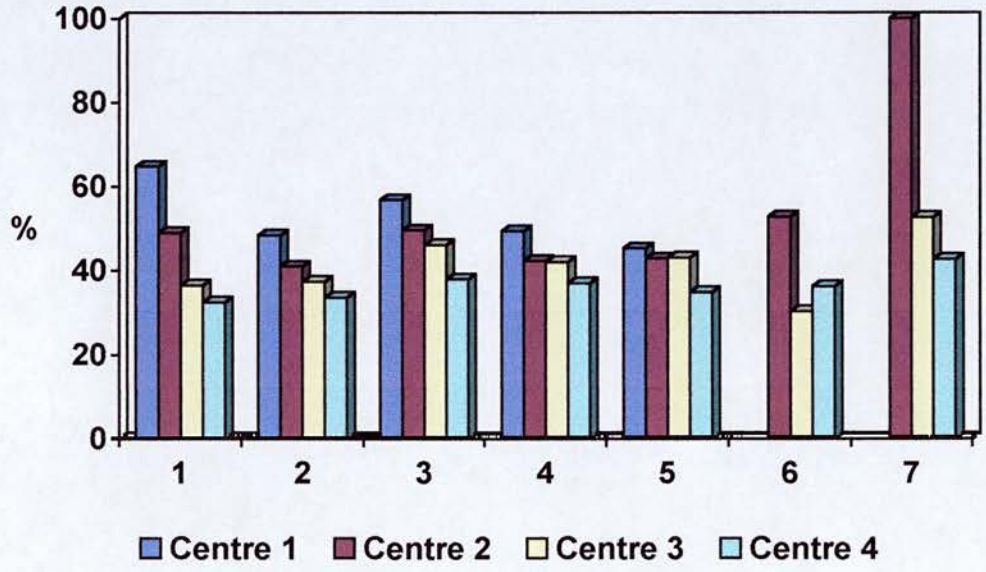


Figure 6.2.6 Proportion of patients listed for transplantation from the total starting dialysis in each centre, according to social deprivation

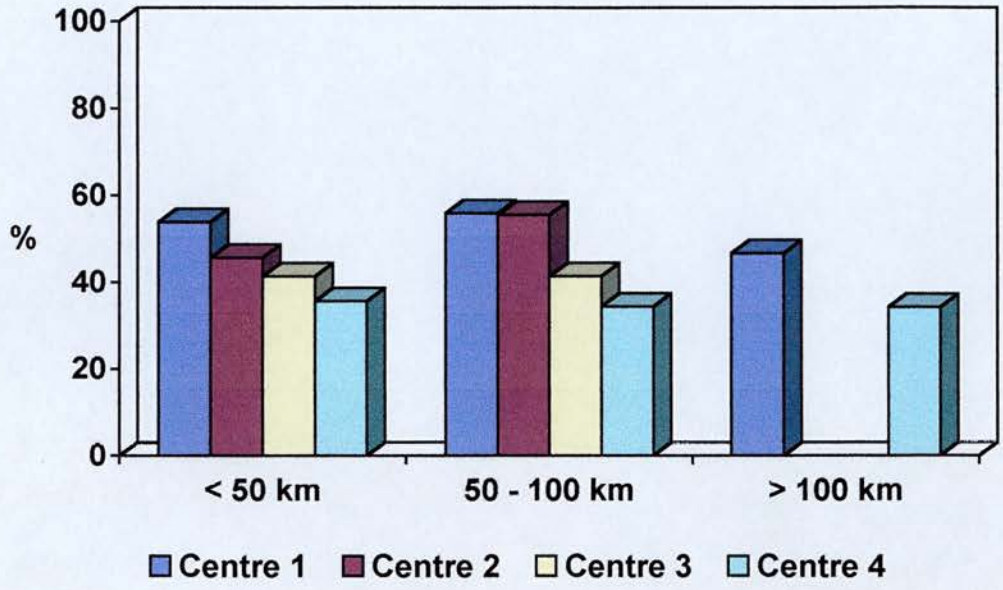


Figure 6.2.7 Proportion of patients listed for transplantation from the total starting dialysis in each centre, according to the distance from the transplant centre (km)

Many of the differences noted so far could be explained by a different comorbidity profile of the patients starting RRT in each centre or who are referred for transplantation from other renal units. Of the total 1022 patients for whom comorbidity was available, 1001 (98%) had at least one comorbid condition in addition to their renal failure.

Data available does not allow comment on the prevalence of comorbidity in each centre or on the proportions of patients with each condition that remain on dialysis, as all patients, for whom information was extracted from the case notes, were listed during the follow-up period. Nevertheless, a comparison of the incidence of individual comorbid conditions among patients listed in each transplant centre (table

6.2.2), provides a good indicator on the kind of comorbidity considered acceptable for the purpose of listing and whether there are major differences between centres.

Factor	Centre 1	Centre 2	Centre 3	Centre 4
Diabetes as a comorbid condition	4 (2.4)	8 (4.7)	7 (2.5)	11 (2.7)
PVD*	16 (9.6)	40 (23.7)	32 (11.4)	38 (9.5)
Hypertension	136 (82.9)	147 (87)	243 (87.1)	358 (89.3)
IHD*	32 (19.3)	50 (29.6)	35 (12.5)	76 (19.1)
Valvular diseases*	20 (11.9)	28 (16.6)	33 (11.8)	34 (8.5)
Pulmonary embolism	2 (1.2)	6 (3.6)	3 (1.1)	4 (1.0)
Arrhythmias	10 (6.0)	12 (7.1)	11 (4.0)	19 (4.8)
Heart failure	7 (4.3)	15 (9.1)	19 (6.9)	27 (6.9)
Left ventricular hypertrophy	57 (35.0)	54 (32.9)	89 (34.1)	121 (31.3)
Other heart	7 (4.2)	11 (6.5)	12 (4.3)	28 (7.03)
Respiratory disease	25 (15.1)	28 (16.7)	32 (11.6)	57 (14.4)
CVD	17 (10.2)	24 (14.2)	20 (7.2)	39 (9.8)
Neoplasia	3 (1.8)	2 (1.2)	9 (3.2)	8 (2.0)
GI disorder*	34 (20.4)	51 (30.2)	45 (16.1)	99 (24.9)
Urological disorders	27 (16.2)	23 (13.6)	45 (16.1)	55 (13.9)
Hyperlipidaemia*	32 (19.3)	16 (9.5)	15 (5.4)	43 (10.8)
Non-smoker*	82 (49.7)	85 (50.9)	183 (66.8)	187(52.2)
Obese*	54 (37.2)	62 (43.4)	115 (43.6)	114 (31.4)
Hyperparathyroidism*	18 (10.8)	16 (9.5)	75 (27.4)	132 (33.1)

Table 6.2.2 Differences in the incidence of comorbid diseases between patients listed in the four transplant centres during the study period (%) (*, $p< 0.05$, statistical significant)

The results presented in table 6.2.2 show that in general, there seem to be an agreement on most of the conditions with a significant impact on the outcome of a transplant, which is illustrated by comparable incidences of hypertension, cardiac arrhythmias, left ventricular hypertrophy and previous neoplasia among patients listed in each centre. As expected, some other risk factors such as peripheral vascular disease and ischaemic heart disease are weighted differently ($p< 0.05$, χ^2) in each transplant centre. As shown in the table, 10-20% of the patients listed in all but one centre will have at least one of the two conditions, with the exception of centre 2 where the assessment is more liberal and between 25% and 30% of the patients joining the transplant waiting list will have peripheral vascular disease and/or ischaemic heart disease.

There is additional evidence for the more liberal practice of listing in centre 2, in the form of a higher incidence, although not statistically significant, of respiratory and cerebro-vascular diseases among patients listed in this centre.

Significant centre variations were also noted with regards to other comorbid conditions such as gastrointestinal pathology, smoking, obesity (BMI≥30), hyperlipidaemia and hyperparathyroidism.

6.2.3 Discussion

Clinical guidelines on assessment for transplantation have been published recently by the American Society of Transplantation and the European Dialysis and Transplant Association (18) (157). These guidelines acknowledge the impact of comorbid conditions on the outcome of transplantation and the need for further investigations in high-risk groups of patients such as elderly and diabetics prior to listing.

In the United Kingdom, there is no consensus on what criteria should be used in the decision of fitness for transplantation and clinical guidelines to provide a standardized approach are long overdue. Individual centres are likely to use the best current practice, but inevitably, there will be significant variations, according to the level of the clinical expertise available in a particular unit, the comorbidity load or the attitude of transplant nephrologists and surgeons towards patient selection. Such differences have been previously documented (199), but it is widely believed that they are evidence based rather than being a true bias towards certain groups of patients.

Throughout the duration of this study in Scotland there were four transplant centres, which enjoyed a close cooperation and exchange of scientific information. In this favourable setting, our aim was to assess whether there are any significant differences in clinical practice, which can be addressed by the implementation of clinical practice guidelines.

The analysis of sociodemographic differences includes all patients listed in the four transplant centres, while comorbidity analysis is restricted only to those patients for

whom data were available. The results of this latter investigation are based on 59% of all patients listed within the study period, but a comparison of centre representation, shown in table 6.2.3, indicates a similar ($p=0.13$, χ^2) distribution of the two populations and therefore it is likely that the centre differences noted here are applicable for all patients listed.

Study groups	Centre 1	Centre 2	Centre 3	Centre 4
All patients (n= 1736)	16.41	11.63	21.77	50.17
Patients with comorbidity collected (n= 1022)	16.34	16.53	27.69	39.43

Table 6.2.3 Distribution of the study populations according to the centre of listing (%).

When the proportions of patients listed out of the total number starting dialysis in each centre were compared, there were substantial differences according to gender, primary renal disease, age, social deprivation, type of first dialysis. It is difficult to understand why there should be differences in listing patients of same gender or patients with a similar deprivation score between the four centres, but it has been suggested that variations in the index of comorbidity across various parts of the country may potentially explain some of these disparities. However, the analysis has shown that for some groups of patients, in particular those aged over 60 years old and the diabetics, there is no consensus on the approach to listing. Centres 1 and 2

list nearly 20% more diabetics or patients aged > 60 years old compared with centres 3 and 4. It can be argued that the latter two centres have a greater workload, and hence in the constraints of the current organ shortage, a much tighter selection process is used to ensure an appropriate use of the available donor kidneys. This is a particularly important and controversial issue, as these patients are usually regarded as high-risk groups, with an increased likelihood of kidney transplant failure or death soon after transplantation. These differences will inevitably create a bias against these groups of patients and raise the issue of equitable access to the renal transplant waiting list across Scotland.

Although there are no uniform criteria for listing, the incidence of most comorbid conditions in patients listed is comparable, of the 40 variables investigated, only 8 being weighted differently by the four centres. This analysis has shown that some of the differences are due to a more liberal approach to listing in centre 2, where patients with a more severe index of comorbidity are allowed to join the list. A few of the factors where significant differences where noted (PVD, IHD, obesity and hyperlipidaemia) are strongly correlated with an increased risk of death following transplantation (168;239).

The demographic structure of the RRT population is changing rapidly, and with an ageing population, it is likely to see more comorbid conditions in the patients assessed for transplantation. Inevitably, listing criteria will have to change and the ability to manage higher risk patients will have to improve. Nevertheless, practical guidelines will ensure that a comparable level of care and an equitable access is available for all patients across Scotland.

The timing of referral for assessment is also an important issue, as patients could be referred at different stages of their disease, when the number of accrued medical conditions could make the all important difference between being accepted as a transplant candidate or being denied access to the transplantation service. This aspect of the practice could not be investigated with data currently available.

This study concentrates on patients already listed and therefore, further investigations are required to determine the prevalence of the comorbid conditions in the ESRD population in each centre and to assess the magnitude of differences between the transplant assessment programmes.

6.2.4 Conclusion

In summary, there are significant differences in the practice of assessing and listing patients for renal transplantation between the four transplant centres in Scotland. The comorbidity index is a significant factor but other issues such as clinical attitudes towards listing may play an important role.

These differences have also highlighted several high-risk groups, such as advanced age and diabetes, where a consensus regarding the optimal listing criteria needs to be reached, in order to ensure the best outcome for patients and an adequate use of donor organs. Further research into the outcome of transplantation compared with dialysis in these groups of patients is required to provide an evidence-based approach for any clinical practice guidelines.

To address some of these issues, two lines of investigation were followed in this chapter: transplantation in elderly and transplantation in diabetics.

6.3 The elderly and transplantation

6.3.1 Introduction

The number of elderly patients accepted in renal replacement programmes is continuously increasing. In Scotland, the annual intake of new ESRD patients over 60 years old has risen from 42% in 1989 to more than 65% in 1999 (32). The largest proportion of this rise is represented by patients aged over 65 years old, who make more than 50% of the total number of new patients in 1999 (figure 6.3.1).

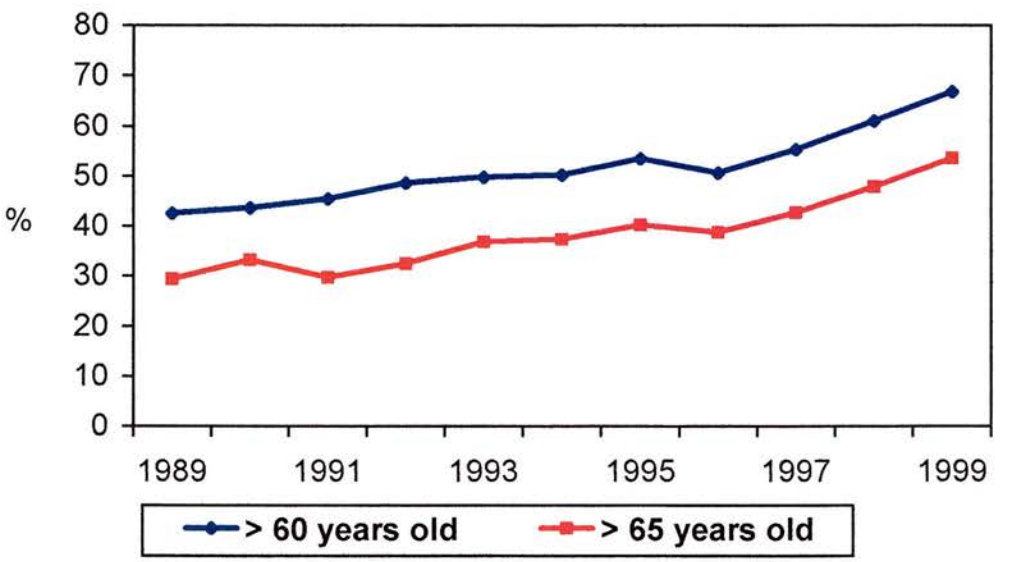


Figure 6.3.1 Proportion of new ESRD patients aged over 60 and 65 years old starting dialysis each year.

A similar trend was noted in the US, where the number of patients over 65 years old requiring RRT doubled in the last decade (240), Australia (241), Japan, Canada and the rest of Europe (31).

On the basis of strong evidence that transplantation is safe and successful (153;242) and survival with a kidney graft exceeds that on dialysis (19;152) even in elderly patients, there is a general agreement that age *per se* does not constitute a contraindication to transplantation. And yet, many centres are still reluctant to accept patients over 60 or 65 years old onto the waiting list [only 3% of patients over 65 years of age are transplanted in the US (125)], as these patients are frail and have more comorbid conditions (150) and their overall life-expectancy is lower than the younger population. In addition, an increased age at the time of transplantation has been shown to have a major influence on long term graft survival (243) and death with a functioning graft accounts for almost 40% of the grafts lost in long term follow-up (151). Nevertheless, this higher post-transplant mortality must be considered against an evident survival advantage of transplantation over dialysis {Chapter 5} (19) and a continuous improvement in the outcome of transplantation in the elderly over time (244) (table 6.3.1).

Study	No. of patients	Patient survival		Graft survival	
		1 yr	5 yr	1 yr	5 yr
Wedel (1980)	38	60	25	60	25
Tesi (1994)	133	88	68.1	82	62
Cantarovitch (1994)	117	92	80	86	80
Lufft (2000)	91	96	74	87	66
Saudan (2001)	48	98	78	93	65

Table 6.3.1 Improvements in patient and graft survival in recipients over 60 years old in the last 20 years ((245-249)

Currently, in the UK there is no age limit for access to transplantation, but only 7.2% of transplant recipients are aged over 65 years old (30). In the present climate of organ shortage, there is a clear bias against the elderly patients, but in the absence of UK based evidence for the outcome of transplantation in this particular age group, it will be difficult to draw practice guidelines to address this issue.

In this national study, two questions were addressed:

1. What is the impact of recipient age on the transplant outcome in Scotland and is there any scope in setting an age limit for a transplant candidate?

2. Is there a survival advantage for transplantation over dialysis in patients over 60 years old who are considered suitable for transplant candidacy?

6.3.2 How old is old for transplantation

6.3.2.1 Methods

All adult patients who started dialysis between 1st of January 1989 and 31st of December 1999 and were transplanted (first graft) until 31st of December 2000 (n=1095) were grouped according to their age at grafting (18-49 years, 50-59 years, 60-64 years and >65 years old). The sociodemographic and comorbidity variables presented in the previous chapters, as well as the level of HLA matching, the length of the cold ischaemic time, patient and graft survival, the incidence of acute rejection episodes and delayed graft function and the causes of death and graft failure were obtained from the SRR and UKT databases and case notes and compared between the four groups. Patient and graft half-life were calculated assuming a constant death rate beyond a year after transplantation (figure 6.3.2) and compared according to patients' age using a Log-rank test.

$$HL = \frac{\ln(2)}{M}$$

ln(2) = natural logarithm of 2

M = Slope of the survival curve assuming a constant death rate post-transplant

Figure 6.3.2 Formula used for calculating patient and graft half life (250)

The risks of death and graft failure were calculated after adjustment for comorbidity and other sociodemographic variables for each group of patients, using a Cox proportional hazards model. Further comparisons were performed using $\chi 2$, T-test, Mann-Whitney U test, Kruskal-Wallis and ANOVA test where appropriate.

6.3.2.2 Results

1095 patients starting dialysis between 1st of January 1989 and 31st of December were transplanted during the study period and followed for up to 11 years, until 31st of December 2000. The demographic characteristics of the study population according to the age at transplantation are shown in table 6.3.2.

The gender ratio was more balanced in the youngest age group compared with the remaining three groups, with a comparable distribution across the social deprivation categories. All groups had a similar prevalence of diabetes as a cause of renal failure, and almost 60% of the patients in each group started replacement therapy on haemodialysis. The time spent on dialysis until transplantation increased significantly with patient's age ($p=0.031$, Kruskal-Wallis test), from a median of 1,3 years in those aged 18-49 years old to almost 2 years in patients aged over 65 years of age. On average, almost one third of all patients switched dialysis modalities until transplantation. This occurred significantly more frequently in the younger patients ($p= 0.034$, χ^2), while 76% of patients aged over 65 years old remained on the initial RRT modality until grafting.

As shown previously, there are significant differences between centres, elderly patients being more likely to be listed in centres 1 and 2.

	18-49 years (n=686)	50-59 years (n=252)	60-64 years (n=82)	>65 years (n=75)	p value
Male:Female ratio	57.9 : 42.1	67.5 : 32.5	64.6 : 35.4	66.7 : 33.3	0.033*
Primary renal disease (%)					0.174
Glomerulonephritis	28.7	30.2	23.2	34.7	
Interstitial nephritis	35.0	34.9	31.7	25.3	
Multisystem disease	11.2	13.5	17.1	18.7	
Diabetes	13.7	8.3	11.0	8.0	
Other	11.4	13.1	17.1	13.3	
Deprivation category (%)					0.62
1	5.0	5.2	6.1	4.0	
2	12.0	13.1	14.6	18.7	
3	22.6	21.8	23.2	30.7	
4	26.1	26.6	29.3	29.3	
5	15.3	16.3	15.9	6.7	
6	12.6	11.5	8.5	9.3	
7	6.4	5.6	2.4	1.3	
HD as 1st RRT (%)	56.5	59.9	62.2	58.6	0.785
Dialysis duration					0.031‡*
Median (years)	1.3	1.33	1.62	1.92	
Number of dialysis switches (%)					0.034*
0	65.7	64.5	61.7	76.0	
1	21.3	21.6	29.6	13.3	
> 2	13.0	13.9	8.7	10.7	
Listing Tx centre (%)					<0.0001*
Centre 1	56.5	23.2	6.5	13.7	
Centre 2	49.5	25.3	7.4	17.9	
Centre 3	62.1	26.0	7.8	4.1	
Centre 4	66.9	21.2	7.7	4.3	

Table 6.3.2 Comparison of baseline characteristics of transplanted patients according to the age at transplantation (*- statistical significant, ‡ - Kruskal Wallis test, all other χ^2 test).

As previously stated, comorbidity was available in approximately 65% of the transplanted patients. A comparison of the incidence of comorbidity among transplant recipients according to their age at grafting (table 6.3.3) shows that there is a significant increase in the incidence of peripheral vascular disease with increased age.

All patients over 50 years of age have a significantly higher incidence of ischaemic heart disease, heart failure, arrhythmias, left ventricular hypertrophy and GI disorders compared with those aged 18-49 years old.

Valvular diseases and pulmonary embolism are most frequent among patients over 65 years of age, while respiratory disease was more often seen in patients aged 60 – 64 years old. Patients in the 18-49 years old group have half of the prevalence of CMV compared with all other groups, while the highest incidence of active or ex-smokers seems to be at the extreme age groups.

In fact, the overall prevalence of comorbid conditions seems to be higher in patients aged 60-64 rather than in those aged over 65 years old. This indicates, that the eldest patients who are eventually transplanted undergo a tight assessment process and only those with limited comorbidity are selected.

All transplants performed in each of the four age groups had comparable levels of HLA matching (table 6.3.4), between 48% and 58% of them being well matched (*i.e.* 000 mismatches [Tier 1] or maximum 2 A and/or B mismatches but no DR mismatches [Tier 2]). Overall, there was a tendency to offer fewer fully matched kidneys to recipients aged > 65 years old, but this was compensated by a higher proportion of Tier 2 (010,010 or 110 mismatches) grafts.

	18-49 years (n=446)	50-59 years (n=160)	60-64 years (n=46)	>65 years (n=55)	p value
Comorbid diabetes (%)	2	1.9	6.7	3.6	0.235
% diabetic cases with end-organ complications	2.6	7.9	9.8	10.5	0.449
PVD (%)	5.0	11.9	16.3	27.3	<0.0001*
Hypertension (%)	86.6	88.8	86.4	87.3	0.919
Mean number of antihypertensive drugs	1.22	1.24	1.09	1.00	0.284‡
IHD (%)	5.9	23.8	40.0	27.3	<0.0001*
Valvular disease (%)	6.5	10.0	8.9	21.8	0.002*
PE (%)	0.2	2.5	2.3	7.3	<0.0001*
Arrhythmias (%)	1.6	4.4	6.8	7.3	0.021*
HF (%)	3.7	7.0	16.7	7.3	0.003*
LV hypertrophy (%)	24.9	32.7	39.0	44.4	0.005*
Other heart disorders (%)	5.0	3.1	11.1	5.5	0.074
Respiratory disease (%)	10.3	15.7	26.7	12.7	0.009*
CVD (%)	8.2	11.3	6.8	5.5	0.491
Previous neoplasia (%)	1.1	4.4	2.3	3.6	0.09
GI disorders (%)	12.7	27.5	38.5	34.5	<0.0001*
Urological disorders (%)	15.0	11.3	13.6	25.5	0.086
Hyperlipidaemia (%)	8.2	8.8	6.7	9.1	0.338
CMV +ve (%)	27.8	48.1	50.0	47.3	<0.001*
Smoker (%)	61.9	49.3	53.7	60.0	<0.001*

Table 6.3.3 Comparison of comorbidity characteristics of transplanted patients according to the age at transplantation (*- statistical significant, ‡ - ANOVA test, all other χ^2 test).

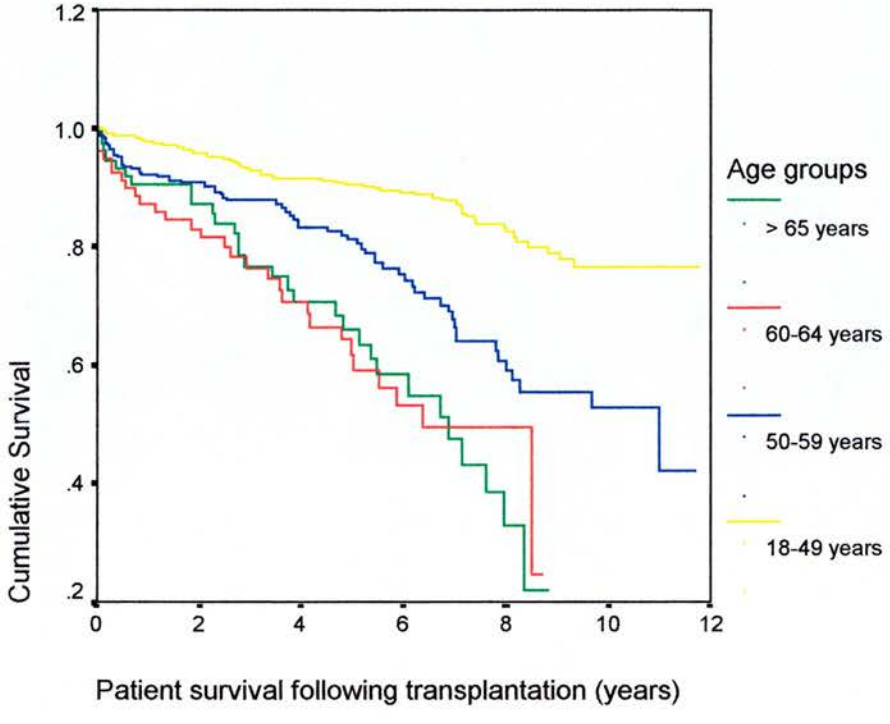
	18-49 years (n=686)	50-59 years (n=252)	60-64 years (n=82)	>65 years (n=75)	p value
Tier (%)					0.1
1	10.8	6.4	14.6	3.8	
2	37.1	44.3	43.9	53.8	
3	52.1	49.3	41.5	42.3	
Donor age					<0.0001‡
Mean (S.D.)	38.0 (14.8)	43.4 (15.2)	48.0 (15.3)	48.2 (16.2)	
Donor gender					0.436
Male/Female	54.0 / 46.0	50.3 / 49.7	63.6 / 36.4	57.4 / 42.6	
CIT					0.004‡
Mean (minutes) (S.D.)	1126 (602.5)	1295 (550.4)	1416 (482.4)	1326 (648.5)	
Acute rejection episodes (%)	34.7	25.2	27.9	23.6	0.092
Chronic rejection (%)	11.9	8.5	7.0	9.1	0.398
DGF (%)	19.2	27.7	20.9	32.7	0.053
Recurrent primary renal disease (%)	2.7	1.9	2.3	0	0.126

Table 6.3.4 Comparison of donor characteristics, level of HLA matching, cold ischaemic time and transplant outcome according to recipient's age at transplantation (*- statistical significant, ‡ - One way ANOVA test, all other χ^2 test).

As expected, the donor age increased, the older the recipient, from 38 years in the younger recipients, to 48 years old in those > 65 years of age, but there was a comparable gender distribution.

Younger patients were transplanted within a shorter cold ischaemic time (mean 1126 minutes), but had a higher incidence of acute rejection episodes, while elderly patients had a higher incidence of delayed graft function, almost reaching statistical significance (p=0.053, χ^2).

All patients had an excellent one-year survival rate (figure 6.3.3). There are no significant differences between the survival curves in the first three years post-transplantation, but as expected, there are substantial differences in the long-term survival between those younger and those older than 60 years of age. Both groups of patients over 60 years of age have comparable survival and even at 9 years post-transplant, almost one quarter of them are still alive.

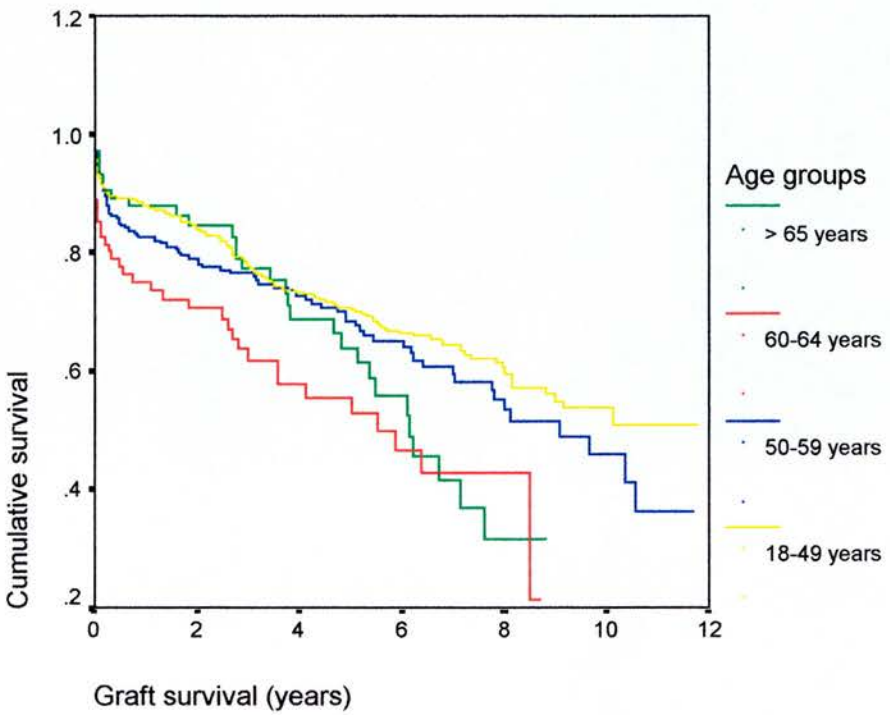


Age group	*1 year*	*3 years*	*5 years*	*10 years*
18-49	98	93	91	77
50-59	92	88	81	53
60-64	87	76	59	25 (9 yr)
>65	91	77	66	33 (9 yr)

Figure 6.3.3 Patient survival following transplantation ($p<0.0001$, Log rank test)

Similar differences were noted for the graft survival (figure 6.3.4), almost 50% of the transplants performed in patients younger than 60 years old functioning at 10 years, in contrast with only 20 to 30% in those over 60 years old.

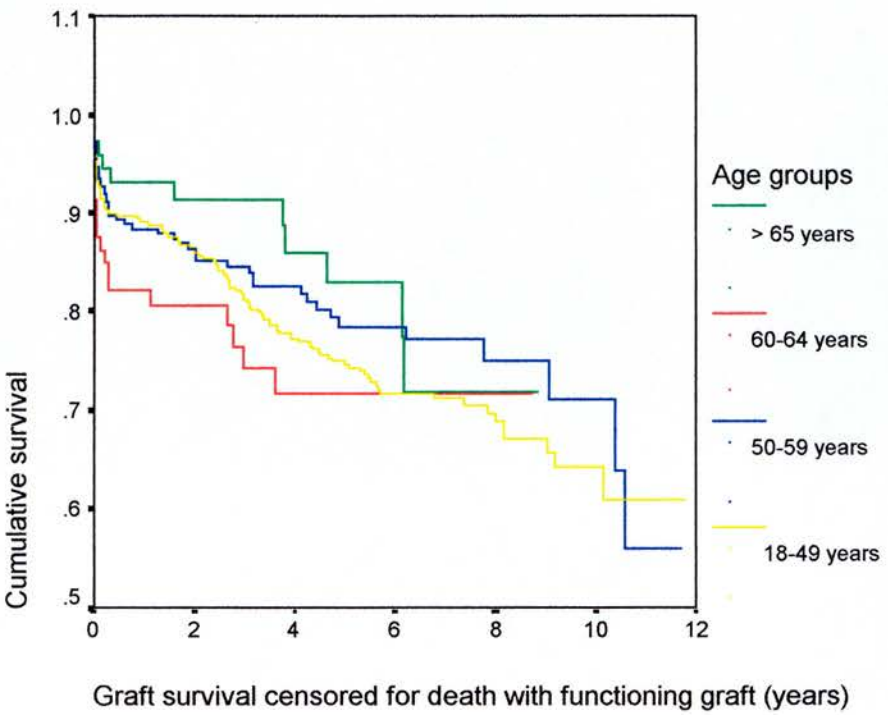
When the two groups of elderly recipients were compared, patients over 65 years of age had a better graft survival throughout the study period.



Age group	*1 year*	*3 years*	*5 years*	*10 years*
18-49	88	78	70	54
50-59	82	76	68	46
60-64	75	62	53	21 (9 yr)
>65	88	77	64	31 (9 yr)

Figure 6.3.4 Graft survival ($p<0.0001$, Log rank test)

This advantage persisted when graft survival censored for death with functioning graft was analysed (figure 6.3.5). In fact, the older group had the best graft survival of the four groups at all time points, but overall, the differences between the study groups were not statistically significant (p=0.2685, Log rank test). This does indicate that a large proportion of elderly patients have functioning grafts at the moment of death.



Age group	*1 year*	*3 years*	*5 years*	*10 years*
18-49	89	81	75	64
50-59	88	85	79	71
60-64	82	74	72	72 (9 yr)
>65	93	91	83	72 (9 yr)

Figure 6.3.5 Graft survival censored for death with functioning graft (p=0.2685, Log rank test)

An examination of the crude death rate (table 6.3.5.) shows a 4 fold increase of the rate from 2.4 per 100 years of patient follow-up in patients age 18-49 years old to 10.35 in those aged > 65 years old. This is further illustrated by the differences in the proportion of patients from each group, dying within the study period. Patient half-life, calculated using the method described earlier, shows a significant reduction in the life expectancy, from 37 years to less than 8 years in patients > 65 years old ($p=0.0001$, χ^2).

	18-49 years (n=686)	**50-59 years (n=252)**	**60-64 years (n=82)**	**>65 years (n=75)**	**p value**
Crude death rate (per 100 years of patient follow-up)	2.4	5.55	10.04	10.35	
Deaths (%)	10.3	24.6	35.4	40.0	<0.0001*
Patient half-life	37.62	17	9.62	7.88	0.0001*
Adjusted RR of death (95%CI)	1	2.37 (1.28-4.39)	2.84 (1.12-7.18)	7.19 (3.54-4.59)	<0.0001*
Graft failure (%)	28.3	34.1	43.9	41.3	0.004*
Graft failure censored for death with functioning graft (%)	22.6	19.4	23.2	16.0	0.457
Graft half-life	9.71	9.00	5.54	6.96	<0.0001*
Adjusted RR of graft failure (95%CI)	1	0.91 (0.59-1.38)	0.63 (0.28-1.42)	1.51 (0.86-2.41)	0.2012

Table 6.3.5 Comparison of patient and graft outcome according to recipient's age at transplantation (*- statistical significant, χ^2 test).

When the relative risk of death, adjusted for comorbidity conditions, was determined, all patient groups had a largely increased risk of death compared with the baseline represented by age group 18-49 years old (table 6.3.5). A similar tendency was observed for graft failures, more than 40% of the grafts in the eldest group being lost during the follow-up, a large proportion of these due to death with functioning graft. Although the overall proportion of lost grafts increases with age, after censoring for death with functioning graft, more grafts appear to be lost in the younger age groups, but these differences are not statistical significant ($p=0.457$, χ^2).

Despite a significant disproportion in the graft half-life between the four groups, a kidney allograft transplanted in patients under 60 years old is likely to function for at least 9 years, while patients over 65 years old enjoy an almost entire dialysis free life following transplantation (graft half life 6.96 and patient half life 7.88, respectively).

A comparison of the relative risk of graft failure adjusted for the confounding comorbidity, showed no significant differences between the four groups of transplanted patients ($p=0.201$, Cox regression analysis, table 6.3.5).

The incidence of death with functioning graft was three times higher in patients aged > 65 years old compared with those aged 18-49 years old, in contrast to immunological failures which had an entirely opposite trend and were most frequent in the youngest age group (table 6.3.6). These differences could be even more striking, if we consider that almost one quarter of the causes of graft failure in the 18-49 year old age group are yet unknown.

Cause of graft failure	18-49 years (n=686)	50-59 years (n=252)	60-64 years (n=82)	>65 years (n=75)	p value
Death with functioning graft (%)	20.6	43.0	47.2	61.3	<0.001*
Immunological failures (%)	34.5	22.1	19.5	16.1	<0.001*
Vascular problems (%)	10.8	9.3	11.2	6.5	0.647
Unknown (%)	22.7	16.3	19.4	6.5	0.002*

Table 6.3.6 Comparison of causes of graft failure according to recipient's age at transplantation (*- statistical significant, χ^2 test).

Significant differences in the proportion of patients dying due to infection or vascular causes were noted between the four groups (table 6.3.7), but these results could be significantly modified, taking into account that between one in four and one in five deaths are not accounted for in each group. If we consider these unknown cases to represent sudden deaths, and therefore have a cardiac origin, this will increase the cardiac causes of death to 50% of all kidney transplants performed in Scotland.

Cause of death	18-49 years (n=686)	50-59 years (n=252)	60-64 years (n=82)	>65 years (n=75)	p value
Cardiac (%)	29.2	33.9	21.4	36.7	0.098
Vascular (%)	11.1	16.1	25.0	3.3	<0.001*
Infection (%)	22.2	12.9	17.9	23.3	0.018*
Cancer (%)	8.3	8.1	3.6	10.0	0.407
Unknown (%)	23.6	24.2	21.4	20.0	0.876

Table 6.3.7 Comparison of causes of death according to patients' age at transplantation (*- statistical significant, χ^2 test).

6.3.2.3 Discussion

The demographics of end stage renal disease demonstrate a constant increase in the age of new patients starting replacement therapy every year. Currently in Scotland, as in many other parts of the world (31;241), more than half of the new patients are aged 65 years old or more, but only few of them will ever be transplanted. These patients represent a particular controversial category (153) and therefore in this analysis we decided to investigate the outcome of transplantation in those over 65 separately from patients aged 60- 64 years old.

Despite a general agreement that age should not represent a contraindication for transplantation, the proportion of kidney transplants performed in elderly patients in UK has not changed much in the last decade (30;251) and many units are still reluctant to accept older patients as transplant candidates. This is clearly illustrated by 10% lower transplant rates in two of the centres, compared with the national average.

Elderly transplant recipients spend a longer time on dialysis and this may be partly due to a lengthier assessment period necessary to confirm suitability for transplantation. It is fairly clear from the present analysis that elderly transplant recipients have a higher index of comorbidity and serious conditions, which shorten the life expectancy, such as cardiovascular and respiratory conditions are more often present in those aged over 60 years old. This does indicate that the lower transplant rates may be a result of the high prevalence of comorbid conditions in this particular age group, which renders most of the patients unsuitable for transplant candidacy.

Older recipients receive kidneys from older donors, but the donor age range is comparable between the four groups, with an upper limit as high as 75 years old. Donor age is a controversial point in kidney transplantation as graft failure rates are higher with increased donor age (96;252). Nevertheless, the use of older donors is considered acceptable due to the scarcity of cadaveric kidneys and good results have been reported when such kidneys were transplanted in aged matched recipients (253). If kidneys from donors as old as 75 years of age can be accepted for implantation, there is no real justification why an increased number of elderly patients could not receive a kidney graft in elderly-for-elderly programmes (215;254), which would eliminate potential allocation obstacles as well as shifting younger donor kidneys to younger recipients.

An older donor age combined with the increased cold ischaemic time for kidneys received by elderly recipients may explain the higher incidence of delayed graft function noticed in these patients. This was counterbalanced by a lower incidence of acute and chronic rejection (although not statistical significant), which is in keeping with a diminished inflammatory and immunological response previously noted in the elderly (245;255).

All groups have excellent one year patient survival rates, ranging between 87% and 98%. The risk of dying increases significantly with age, and beyond three years there is a substantial survival benefit for younger patients, while the two groups of patients aged over 60 years old have comparable, but diminished survival rates. A similar trend is noticed for the graft survival, with comparable one-year figures (75% to 88%) and a long-term advantage for younger recipients. The crude rate of graft loss increases with age, but as reported elsewhere (245;256;257), a significant proportion

of the grafts in elderly patients are lost due to patient death. This should not necessarily be interpreted as a waste of kidneys, as immunological failures are less common in patients over 60 years of age (247;248) and the overall risk of graft loss is comparable irrespective of the recipient's age (258;259). It is important to note that while in the youngest group the estimated graft half life is nearly 10 years, against an estimated patient half life of 37 years, a 7 years graft half life in the eldest group ensures a dialysis free life in the context of a half life of eight years, offering a substantial improvement in the quality of life (25).

The patient and graft survival probabilities noted here are comparable with previous reports (96;153;248;260;261) and 60-66% respectively 55-64% 5 years patient and graft survival in patients over 60 are considered the norm. In addition, the controlled comparison performed in this study has shown that results in patients over 65 years of age are similar to those obtained in patients aged 60-64 and therefore these patients should be considered for transplantation.

The assessment process is critical to the success of transplantation in the elderly and there is evidence that with a strict evaluation, 80% 5-year patient and graft survival in these patients is achievable (245). The incidence of death due to cardiovascular diseases or infection was not significantly different in the four groups in this study. This suggests that elderly patients, despite a higher prevalence of these conditions, when correctly assessed and selected may not exhibit a higher risk of death as a direct result of them.

6.3.2.4 Conclusion

Older patients with ESRD present health care professionals with a significant challenge and many management issues such as the timing or choice of replacement therapy or the assessment protocol remain subject to debate. With a prevailing shortage of organs, kidney transplantation should not be used indiscriminately in the elderly, nor should the elderly be denied access simply on the basis of age. Careful assessment of "biological" rather than "chronological" age should be used on an individual basis instead of applying rigid age limits, as there is little doubt from this analysis that transplantation even in those of advanced age is successful and provides dialysis-free and good quality of remaining life.

6.3.3 Transplantation versus dialysis in elderly recipients

6.3.3.1 Methods

All patients 60 years old or over accepted onto the waiting list and who started dialysis between 1st of January 1989 and 31st of December 1999 were selected for this analysis. 15 patients who were listed pre-dialysis were excluded from the analysis. Socio-demographic, listing, transplant data as well as comorbidity were obtained from the national renal (SRR) and transplant (UKT) databases and case-notes review. Survival was compared between those who were transplanted and those who were listed but remained on dialysis by the end of the follow-up period (31st of December 2000). In calculating the survival curve for transplantation, follow-up was considered from the date of transplant. For the dialysis curve, all patients on dialysis were considered and the follow-up time started at the moment of listing, but those patients who received a transplant were censored at the time of grafting. Survival at 1, 3, 5 and 8.5 years was estimated for each treatment modality using the Kaplan Meyer method and a Log-rank test to determine the statistical significance of the findings. The rates of death per 100 patient-year were determined for transplantation and dialysis. A time-dependant Cox regression analysis adjusted for sociodemographic variables (gender, age, social deprivation, primary renal disease, distance from patient's home to the transplant centre, time on dialysis pre-listing)

was employed to calculate the relative rate of death for transplantation versus dialysis, allowing for the changes in the treatment status (dialysis or transplant) during the follow-up period. For the purpose of this analysis, an intention to treat method was applied, whereby all patients were considered to be on the waiting list at any time, until death, end of study or transplantation (whichever occurred first), irrespective of suspension and removal periods. Transplant recipients contributed survival towards transplantation until the graft failed. Any subsequent length of life was counted towards survival on dialysis. Survival was considered from the moment of listing for transplantation. Data on comorbidity illnesses was available in 60% of all patients and the distribution of the comorbidity burden was compared between transplant recipients and those who remained on dialysis. A separate time-dependant Cox regression analysis, adjusted for sociodemographic and comorbidity variables was built and the results compared with the time-dependant model adjusted only for sociodemographic factors. $\chi 2$, Student t-test, Kruskal-Wallis and Fisher's exact tests were used to estimate the statistical significances of any other differences.

6.3.3.2 Results

340 patients over 60 years old were listed during the study period. 137 (40.3%) of them received a first transplant, while the remaining 203 (59.7%) continued to undergo dialysis, in stark contrast to 957 (68.6%) of the 1396 patients under the age of 60 who were listed and transplanted in the same period.

A comparison of the baseline demographics at the time of listing for patients over 60 years old, according to their subsequent treatment status is shown in table 6.3.8. Both genders and all social deprivation categories were equally represented among patients who were transplanted and those who remained on dialysis, but fewer patients with diabetes or multisystem diseases leading to ESRD received a kidney graft.

The transplant recipients were listed at a younger age (64 years versus 66 years), spent half the time on the active waiting list (250 days versus 530 days) and were on dialysis for a similar length of time (7 months) compared to those who were listed but remained on dialysis. In both groups nearly two thirds of the patients had haemodialysis as the first type of replacement therapy and a similar proportion remained on the initial dialysis modality until listing. The transplant recipients lived significantly closer to the transplant centre compared with those who were listed but not transplanted.

	Remain on dialysis n=197	Transplant n=128	p value
Gender (%)			0.352‡
Male	59.4	64.8	
Female	40.6	35.2	
Median age at listing (I.Q.R.)	66.3 (63.0-72.9)	64.0 (58.5-69.5)	<0.0001* #
Primary renal disease (%)			0.029*
Glomerulonephritis	19.8	30.5	
Interstitial nephritis	20.8	28.1	
Multisystem disease	23.4	18.8	
Diabetes	11.2	7.8	
Other	24.9	14.8	
Deprivation category (%)			0.136
1	9.6	6.3	
2	11.7	18.8	
3	35.0	23.4	
4	22.3	30.5	
5	11.2	9.4	
6	7.6	9.4	
7	2.5	2.3	
HD as first dialysis method (%)	66.3	60.2	0.288‡
Median dialysis duration pre-listing (I.Q.R.) (yr)	0.65 (0.29-1.01)	0.65 (0.24-0.96)	0.688 #
Number of dialysis switches until listing (%)			0.079
0	69.4	76.6	
1	21.9	16.4	
>2	8.7	7.0	
Distance (km) to the transplant centre (mean ±SEM)	42.45±4.6	27.22±3.65	0.043* #
Time on active waiting list (days)	529 (181-877)	252.5 (21-484)	<0.0001* #

Table 6.3.8 Baseline demographics for patients on dialysis and transplant recipients who were 60 years or older at listing (*-statistical significant, $p<0.05$), (‡- Fisher's exact test, # - Mann Whitney U test, all other χ^2)

An extensive comorbidity index was available for 191 (60%) of all patients. Although all patients went through the assessment process and were deemed suitable for transplantation, there was a higher incidence of ischaemic heart diseases, cardiac arrhythmias and cerebrovascular diseases in patients who were listed but remained on dialysis until the end of the follow-up period. All the other associated conditions were equally distributed between the two groups.

	Remain on dialysis n=107	Transplanted n=84	p value
Comorbid diabetes (%)	4.7	4.8	1.000
PVD (%)	25.2	21.7	0.609
Hypertension (%)	84.1	85.5	0.841
IHD (%)	45.4	28.6	0.024*
Valvular disease (%)	28.7	16.7	0.121‡
PE (%)	2.8	6.0	0.301
Arrhythmias (%)	17.6	6.0	0.016*
HF (%)	13.1	10.8	0.662
LV hypertrophy (%)	42.1	43.2	0.883
Other heart disorders (%)	6.5	7.1	1.000
Respiratory disease (%)	17.0	20.2	0.578
CVD (%)	15.1	4.8	0.03*
Previous neoplasia (%)	1.9	2.4	1.000
GI disorders (%)	32.4	38.1	0447
Urological disorders (%)	13.9	22.2	0.130
Smoker (%)	55.3	43.9	0.089‡

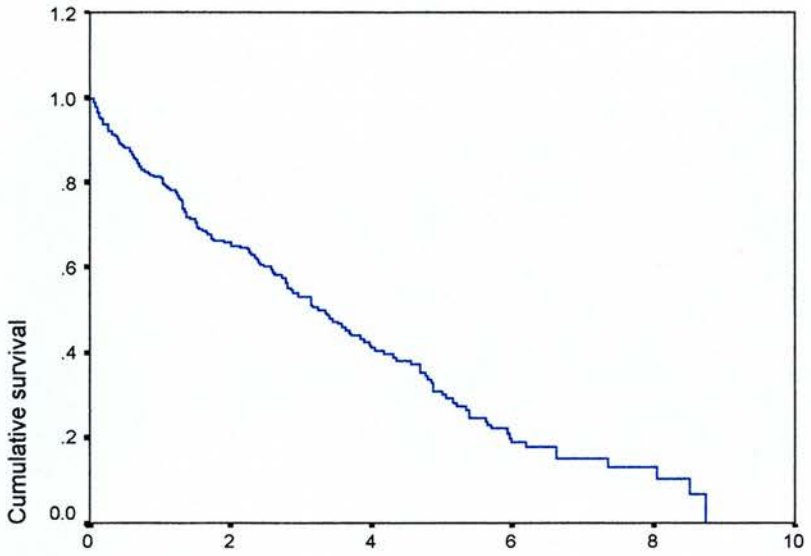
Table 6.3.9 Comorbidity for patients on dialysis and transplant recipients who were $\geq$ 60 years old when listed (*-statistical significant, $p<0.05$), (‡ - χ^2, all other Fisher's exact test)

During the follow-up 116 (58.9%) dialysis patients and 52 (40.6%) transplant recipients died ($p<0.0001$, χ^2). The overall rate of death was 16 per 100 patient-year in the dialysis group and 7 per 100 patient-years for transplant recipients with a functioning graft. There were no significant differences ($p=0.211$, χ^2) between the various causes of death in both groups of patients (table 6.3.10).

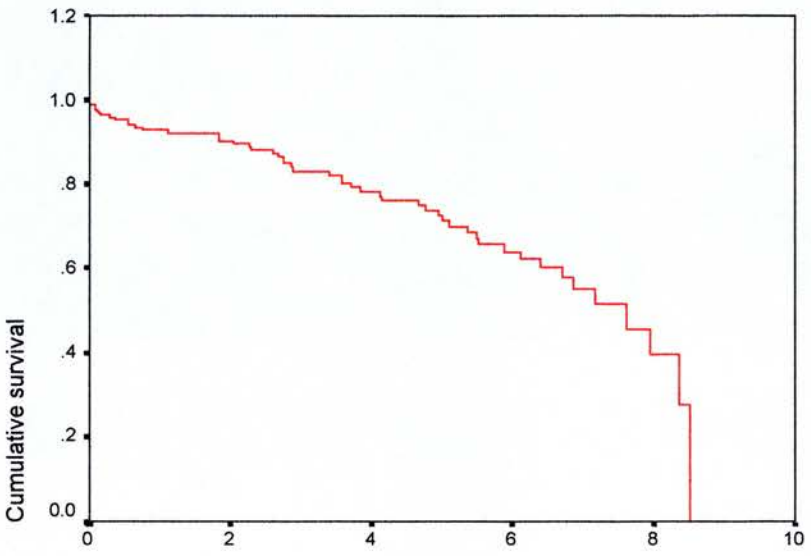
Cause of death	**Remain on dialysis n=116**	**Transplanted n=52**
Cardiovascular (%)	47.4	43.2
Infection (%)	17.2	17.6
Cancer (%)	6.0	7.8
GI (%)	1.8	5.9
Unknown (%)	21.6	21.6

Table 6.3.10 Causes of death in patients on dialysis and transplant recipients.

The survival curve for dialysis patients is shown in figure 6.3.6.a. Survival is expressed from the listing moment and it is censored at the time of transplantation for those patients that received a graft. Survival for the transplant recipients, from the moment of grafting is shown in figure 6.3.6.b. Although, the curves are not directly comparable, having a different starting point, they provide a good indicator of the survival advantage for transplantation, bearing in mind that during this study, in Scotland patients waited on average 17 months prior to receiving a kidney allograft.



a. Survial for dialysis patients (censored at transplantation) (years)



b. Survival for transplanted patients (years)

	Transplant	*Dialysis*
1 year	93%	81%
3 years	83%	53%
5 years	70%	30%
8.5 years	27%	6%

Figure 6.3.6.a&b Patient survival (Kaplan Meier) and proportion surviving at 1, 3, 5 and 8.5 years in each group, adjusted for sociodemographic factors

Using a time-dependant Cox model to control for the variable time until transplantation, a long-term (beyond one year) relative risk of death of 0.37 (95%CI: 0.24 - 0.57) was determined in favour of transplantation. In other words, after adjusting for gender, age at listing, type of renal disease, social deprivation and distance between patient's home and the transplant centre, transplant recipients have a 63% lower risk of dying at one year after transplantation compared with patients on dialysis. There is an increased risk of death (although not statistical significant) immediately following transplantation as shown in table 6.3.11. The risk evens out during the first year post-transplant and from there onwards there is an increased likelihood of survival for the transplant recipients. When the sample was restricted to those for whom comorbidity data was available, the hazard ratio associated with transplantation was 0.30 (95% CI: 0.16-0.56), but the same trend for the risk of death as for the whole study population was observed (table 6.3.11).

Subgroup	*< 30 days*	*31 – 365 days*	*> 365 days*
All patients	2.35 (0.73-7.59)	0.73 (0.38-1.42)	0.37 (0.24-0.57)*
Patients with comorbidity data	1.52 (0.20-11.81)	0.54 (0.19-1.54)	0.30 (0.16-0.56)*

Table 6.3.11 The relative risk of death following transplantation compared with dialysis patients at 30 days, within one year and beyond one year (Time-dependant Cox regression analysis, * = statistical significant, $p<0.05$)

These results do not take into account whether the transplants fail and therefore they estimate only the impact of receiving a transplant on the likelihood of survival. To estimate the impact of a transplant with a functioning graft on survival, a similar analysis, but censored at graft failure, was carried out (table 6.3.12). The results confirm a higher initial postoperative risk associated with transplantation, which was suggested in the previous table, and describe an identical trend with a 65% improvement in survival beyond a year offered by kidney transplantation.

Subgroup	*< 30 days*	*31 – 365 days*	*> 365 days*
All patients	4.91 (2.09-11.52)*	0.71 (0.35-1.41)	0.35 (0.22-0.54)*
Patients with comorbidity data	5.03 (1.43-17.73)*	0.43 (0.13-1.40)	0.27 (0.14-0.52)*

Table 6.3.12 The relative risk of death following transplantation compared with dialysis patients at 30 days, within one year and beyond one year (Time-dependant Cox regression analysis, * = statistical significant, $p<0.05$), (transplant censored at graft failure).

6.3.3.3 Discussion

The number of elderly patients requiring replacement therapy has increased worldwide and this trend is likely to continue in the next decade (31;32;262). There is a substantial amount of evidence that transplantation is very effective in patients aged 60 and over (244;245;247;248;260) and provides a quality of life superior to that on dialysis (25;263) but with the current shortage of organs however, it is sometimes difficult to justify the use of a donor kidney in a patient with a limited life expectancy, such as the elderly patient. Therefore it is important to demonstrate that in the current era of significant improvements in survival on both forms of therapy (264), transplantation does indeed provide a major advantage compared to dialysis. The results of this study present strong evidence that renal transplantation in Scotland confers a substantial survival advantage over dialysis in patients over 60 years old who are considered suitable for listing and transplantation.

Elderly patients who remain on dialysis have a death rate two times higher than transplant recipients. Similar findings have been reported from single centre (258) as well as population based investigations (22). This lower death rate translates into excellent patient survival after transplantation at 93%, 70% and 27% at one, five and 8.5 years respectively. In contrast, survival on dialysis is much lower, at 81%, 30% and 6% at the same intervals. The survival rates reported in this study are comparable with those found by other authors (22;153;265), and although care must be taken when comparing results from various studies, as the approach towards the covariates may be different, in general comparisons are usually achievable. Early studies

comparing the outcome of transplantation with that of dialysis in the elderly revealed contradictory findings. Some of them (266;267) identified a higher mortality rate for transplantation, while others (227;268) found no difference in long term patient survival. Other studies reported a better short term (269) and long term (270) survival following transplantation. It is essential to note that such historical comparisons are confounded by several factors (256). First of all survival after transplantation cannot be directly compared with survival on dialysis from waiting list registration, as the starting points are different and those patients who receive a transplant must survive long enough to do so. In addition, comparisons between patients on dialysis, irrespective of their listing status and transplant recipients will inherently be biased towards transplantation, as not all patients on RRT will be suitable candidates for a kidney graft. Thirdly, transplantation itself is time-dependant and accordingly, any change in the treatment status must be taken into account (21) and comparative survival analyses should include only listed patients and start at the moment of registration onto the waiting list.

Using a time-dependant Cox regression analysis, the risk of dying beyond one year following transplantation was found to be 70% lower than on dialysis (RR=0.30, 95%CI: 0.13-0.70). This risk is increased in the immediate postoperative period (although not statistically significant) and becomes comparable with the risk of death on dialysis during the first year, before decreasing to a beneficial long-term effect. A similar finding was reported by Wolfe et al (19) who noted a 61% lower risk of death at 18 months post-transplant compared with dialysis for patients aged 60-74 years old. The survival advantage was identical when the study sample was restricted to those in whom comorbidity data was available and when the model was adjusted for

these additional factors. This indicates that the survival benefit estimated in population-based studies such as the current one, or the one by Wolfe et al (19) where a full comorbidity profile in all patients is missing, may be slightly over-estimated. Such differences were reported by Schaubel et al (22) who noted that the greatest survival benefit for transplantation is attained among older ESRD patients with no comorbid illnesses. The lack of comparable comorbidity data in most of the studies to date is a potential source of bias in any comparative analyses of the results published so far.

The impact of comorbidity highlights the crucial role of the assessment process in obtaining the best results (18;245). This study has shown that although all patients were considered suitable for transplantation, those who were eventually selected as recipients tended to be younger and had less diabetes and multisystem diseases leading to ESRD. In addition, ischaemic heart disease, arrhythmias and cerebrovascular diseases were more frequent in those who remained on dialysis indicating that these factors have an important role in deciding who receives a kidney transplant. It is also important to highlight that these elderly patients, despite being considered suitable potential recipients, have a high incidence of comorbid conditions illustrated by 80% hypertension, 40% left ventricular hypertrophy, 30% ischaemic heart disease, 20% peripheral vascular disease and 20% respiratory diseases which will need a huge amount of expertise and resources to manage. Clearly, as the comorbidity conditions were not available for all patients it is difficult to extrapolate these findings to the whole patient population, but even if one hypothesises that the remaining 40% of patients had no comorbidity at all, we are still faced with a large proportion of high-risk patients. In addition, this comorbidity

burden has a significant impact on the causes and rates of death, nearly 60% of patients in both groups succumbing to cardiovascular and infectious causes, as previously reported (258).

6.3.3.4 Conclusion

In conclusion, this analysis of Scottish data suggests that elderly transplant recipients have a significant survival advantage over similar patients who are considered suitable for transplantation but remain on dialysis. Transplantation in the elderly is not only safe and successful, but it is also the best treatment available to these patients and therefore patients should not be denied this option purely on the basis of age. A careful evaluation of renal disease's stage and comorbid illnesses and an individual assessment of the likelihood of surviving on either treatment modalities should form the basis of the medical decision and an informed choice for the patients.

6.4 Patients with diabetes and transplantation

6.4.1 Introduction

Diabetes mellitus represents a significant problem in the Western society. The incidence is increasing continuously and 221 million people are likely to be affected by 2010 (271). Huge financial and human resources are spent to target at risk populations and to deal with the devastating effects of the disease, which often leads to premature death from macrovascular disease. Diabetes mellitus is today the leading cause of renal failure in Japan, Scandinavia and the USA (31;272) and the incidence is rising in most European countries (273;274). Renal replacement for end-stage renal failure is more frequent in those with type I (insulin-dependent) diabetes in Northern Europe and the UK, whilst in Central and Southern Europe those with Type 2 diabetes comprise the majority of diabetics on RRT (275). The increasing number of patients with type 2 diabetes will represent a significant burden for the future of any transplant programme.

Until the development of transplantation, diabetic nephropathy led to a dramatic reduction in the life expectancy for most of these patients, as survival on dialysis was and still is poor (276). A renal transplant will not cure the disease, but will provide a better quality of life and a significantly longer life than dialysis (19;21) {Chapter 4}. Data exists to suggest that renal transplantation may actually improve some of the

other end-organ complications of the disease (277). Patients with diabetes are considered to be high-risk candidates for a kidney transplant as most studies reported to date have shown a poorer outcome for diabetic patients compared with non-diabetics (278-281). This is not only due to the disease itself but also to a significant amount of comorbid illnesses (274), which will lead to a poor long-term outcome, mainly due to advanced disease related complications (281-284). However, due to advances in the transplant care as well as the management of complicated diabetes, success rates comparable with non-diabetics are now attainable (285;286).

With an excellent long-term survival, simultaneous kidney-pancreas (287) or more recently, islet cell transplantation (288), offers additional treatment options for these patients. However which patients are suitable (289), when should they be referred and which are the indications for one or another form of therapy must be based on individual patient assessment in order to maximise the benefit and ensure and optimal use of the resources. By the time of referral and full assessment, a large proportion of these patients will be unsuitable for a large undertaking such as a simultaneous kidney-pancreas transplant and therefore a renal transplant remains the reasonable choice of treatment.

One of the questions we need to answer is how useful and successful is renal transplantation in these patients. Although high-risk patients, most type I diabetics are young and therefore it would be difficult to argue against not transplanting, even if the life expectancy is shorter. The question is even more difficult to answer for patients with type 2 diabetes, who are likely to be older and have significantly more comorbid conditions. It can be argued that these patients should be deferred from

transplantation, but recent investigations have shown outcomes comparable with type I diabetes (290).

On this background, an investigation was designed to examine the proportion of patients with diabetes in a cohort of new ESRD patients in Scotland and to determine the success of renal transplantation over the last decade in managing these patients. This will allow conclusions on the role and place of renal transplantation in the management of diabetic patients.

6.4.2 Methods

All adult patients (n=4532) starting dialysis during the study period (1st of January 1989 and 31st of December 1999) were grouped according to their diabetic status. For the purpose of this study a patient was considered diabetic only if diabetes was the primary renal disease.

As described in the previous chapters, data was collected from the SRR and UKT databases as well as case-notes review.

A comparison between listing and transplantation rates as well as demographic differences between the two groups was carried out. The outcome variables (patient survival, graft survival, acute rejection, delayed graft function, causes of death and graft failure) were analysed for those patients with diabetes and compared with the remaining patients.

Comorbid illnesses were collected for 1022 patients at the time of listing for transplantation and a comparison of the disease prevalence between diabetics and non-diabetics admitted onto the waiting list was carried out. This subset represented 59% of all patients listed and had an identical distribution between diabetics and non-diabetics as the whole study population (figure 6.4.1, p=0.369, Fisher's exact test), and therefore the results could be considered representative.

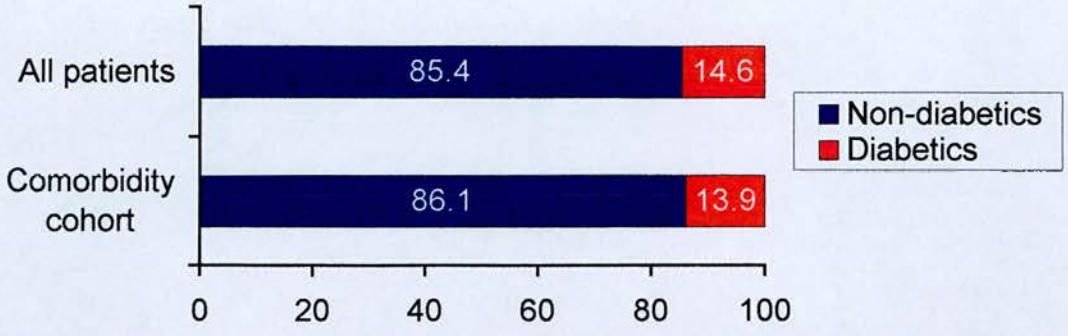


Figure 6.4.1 Proportion of patients with diabetes in the two populations

Finally, a comparison of the survival on transplantation versus dialysis in patients with diabetes was performed. Survival curves were obtained using a Kaplan Meier analysis and statistical significance was estimated using a Log-rank test. A time-dependant Cox regression analysis was used to estimate the relative risk of death for transplantation versus dialysis at 30 days, within the first year and beyond the first year following transplantation. χ^2, Fisher's exact test, T-test, ANOVA and Kruskal-Wallis test were used to quantify the statistical significance of all the other differences noted in this study.

6.4.3 Results

4532 adult patients that started dialysis between 1st of January 1989 and 31st of December 1999 were included in this analysis. 704 patients (15.5%) had diabetes mellitus recorded as their cause of renal failure, two thirds having type I diabetes (n = 474) while the remaining 230 (32%) had type 2 diabetes. 253 (36%) of the diabetics were listed and only 130 (18%) were transplanted. The proportions of patients with diabetes among the 1736 listed patients and the 1095 patients that were transplanted during the follow-up period are illustrated in figure 6.4.2.

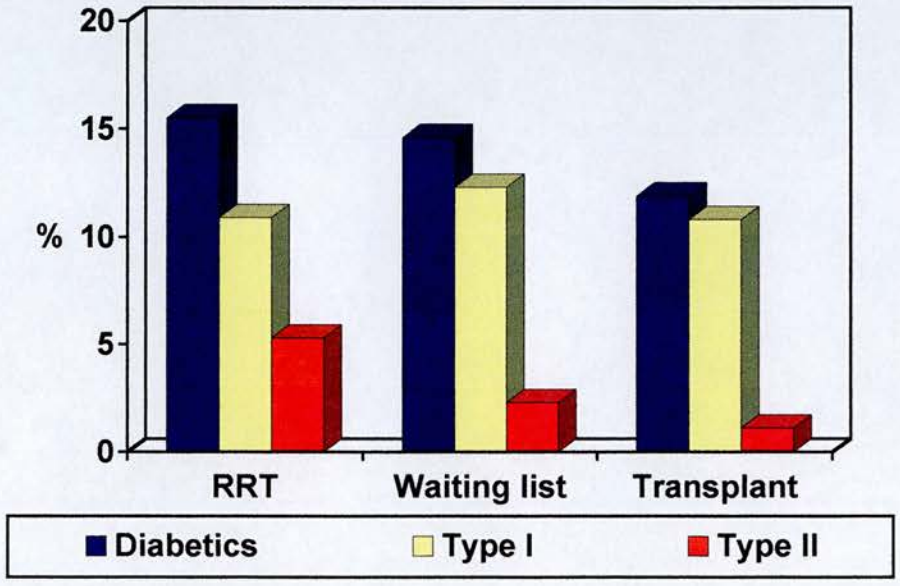


Figure 6.4.2 Overall incidence of diabetes and of the two types in the RRT, waiting list and transplant populations

A significantly lower proportion of diabetic patients were listed ($p=0.020$, χ^2) and transplanted ($p<0.0001$, χ^2) compared with non-diabetics. On close examination, the proportion of type I diabetics that were listed and transplanted remained relatively constant and most of the reduction in listing and transplantation rates is due to type 2 diabetic patients. Only 5% of all type 2 diabetic patients starting RRT were transplanted during the study period.

Diabetic patients are accepted onto the waiting list having significantly more comorbid conditions compared with the non-diabetic patients (table 6.4.1). Diabetic transplant candidates have almost five times more peripheral vascular disease and twice as much ischaemic heart disease compared to non-diabetic patients ($p<0.0001$, χ^2). One in six listed diabetic patients has advanced peripheral vascular disease and almost one in ten has had a myocardial infarction prior to being accepted onto the waiting list. Nearly half of these patients are obese (BMI>35) - significantly more than non-diabetics - in addition to 40% of them having left ventricular hypertrophy and a smoking habit.

Comorbid condition	Non-diabetics	Diabetics	p value
PVD (%)	8.0	39.7	<0.0001*
Ischaemic ulcer/rest pain	0.3	5.7	
Revascularization procedures	0.9	3.5	
Amputations	0.001	6.38	
Hypertension (%)	85.8	96.4	<0.0001*
IHD (%)	16.3	36.2	<0.0001*
Myocardial infarction	3.3	8.5	
Valvular disease (%)	11.6	9.9	0.663‡
PE (%)	1.6	0.7	0.708
Arrhythmias (%)	5.1	5.7	0.685
HF (%)	6.3	10.1	0.105
LV hypertrophy (%)	31.8	39.9	0.064
Other heart disorders (%)	5.0	9.9	0.058‡
Respiratory disease (%)	14.8	10.0	0.150
CVD (%)	9.2	14.2	0.069
GI disorders (%)	22.9	20.6	0.588
Urological disorders (%)	15.8	8.5	0.021*
Smoker (%)	44.0	45.9	0.747‡
CMV+ve (%)	36.0	41.1	0.468‡
EBV+ve (%)	12.4	15.6	0.252‡
Obese (%)	36.2	47.2	<0.0001*

Table 6.4.1 Comorbidity conditions present in patients listed for transplantation, according to their diabetic status (*-statistical significant, $p<0.05$), (‡ - χ^2, all other Fisher's exact test)

This higher comorbidity index has a significant impact on the rate of death on dialysis on the waiting list as well as after transplantation (table 6.4.2). While on the waiting list, diabetic patients have a three times higher rate of death compared with non-diabetics. In both groups, there is a significant reduction in the rate of death after transplantation, but the magnitude of the effect is greater in non-diabetics. If transplant survival is censored at the time of graft failure, the death rates are improved (6.69 for diabetics and 2.37 for non-diabetics), but the rate is still almost three times higher in diabetic transplant recipients.

	Waiting list		Tx group	
	Number	Death rate	Number	Death rate
Diabetics	253	20.63	130	7.91
Non-diabetics	1483	7.08	965	3.64

Table 6.4.2 Death rate per 100 patient-years for diabetics versus non-diabetics on renal replacement therapy, after placement on the waiting list and with a functioning transplant.

In comparing all transplant recipients according to their diabetic status, the baseline demographics are well matched (table 6.4.3). The two groups have a similar gender, age at transplantation, social demographic and geographic distribution. Both groups spent an equal length of time on dialysis, but a higher proportion of diabetic patients

started RRT on peritoneal dialysis, probably due to an increased risk for HD due to diabetic microangiopathy.

	Non-diabetics n=965	Diabetics n=130	p value
Gender (%)			0.152‡
Male	62.0	55.4	
Female	38.0	44.6	
Median age at transplantation (I.Q.R.)	44.1 (32.8-55.5)	40.6 (32.3-48.9)	0.336 #
Deprivation category (%)			0.056
1	5.2	3.9	
2	12.4	16.3	
3	21.8	32.6	
4	27.9	17.8	
5	15.2	13.2	
6	11.8	11.6	
7	5.7	4.7	
HD as first dialysis method (%)	62.0	43.8	<0.0001*‡
Median dialysis duration pre-listing (I.Q.R.) (yr)	0.4 (0.1-0.7)	0.4 (0.2-0.6)	0.749 #
Number of dialysis switches until transplantation (%)			0.088
0	64.9	72.9	
1	22.6	13.2	
>2	12.5	13.9	
Median distance (km) to the transplant centre (IQR)	18.3 (4.02-32.7)	20.5 (0.5-40.6)	0.282 #
Time on active waiting list (days)	315 (37-593)	248.5 (1-538)	0.426 #

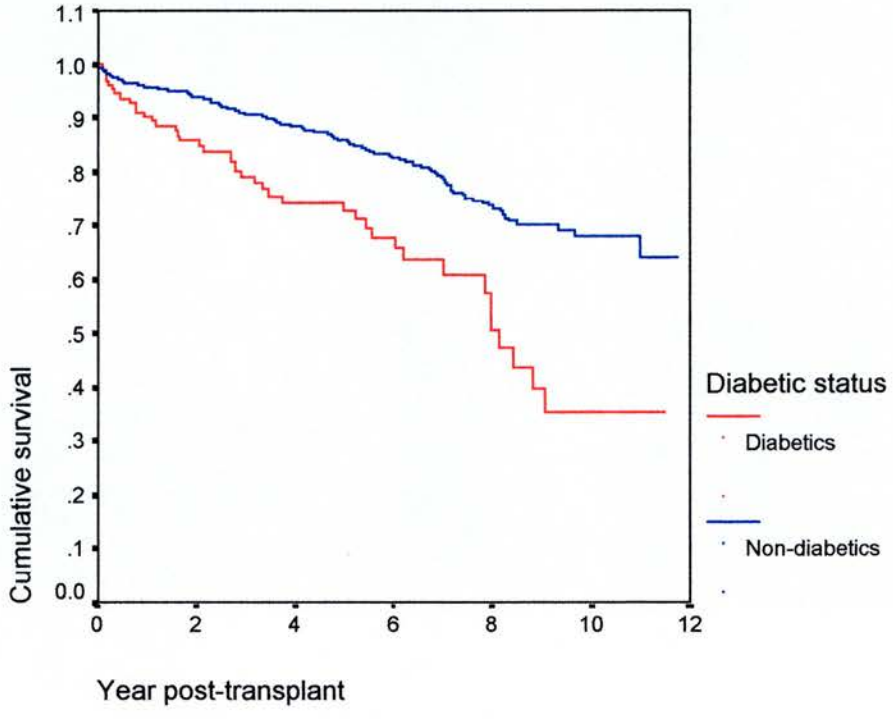
Table 6.4.3 Baseline demographics for the transplant recipients according to their diabetic status (*-statistical significant, $p<0.05$), (‡- Fisher's exact test, # - Mann Whitney U test, all other χ^2)

All patients, irrespective of their diabetic status, received comparable matched kidney grafts, from donors with a mean age of 40 years old and within an average cold ischaemic time of 20 hours. The incidence of acute and chronic rejection as well as delayed graft function was comparable between the two groups as shown in table 6.4.4.

	Non-diabetics n=965	**Diabetics n=130**	**p value**
Tier (%)			0.208
1	9.1	13.4	
2	41.5	31.3	
3	44.2	55.2	
Donor age			0.575‡
Mean (S.D.)	40.8 (15.7)	39.7 (13.7)	
Donor gender			0.628
Male/Female	53.7 / 46.3	57.1 / 42.9	
CIT			0.845‡
Mean (minutes)	1196	1178	
(S.D.)	(593)	(610)	
Acute rejection episodes (%)	31.2	31.6	0.779
Chronic rejection (%)	10.6	10.5	0.778
DGF (%)	22.6	19.7	0.573

Table 6.4.4 Comparison of transplant indicators according to the diabetic status of the recipient (‡ Two samples t-test, all other χ^2 test).

Patient survival following transplantation is significantly better ($p<0.0001$, Log rank test) for non-diabetic patients (mean: 9.6 years, 95%CI: 9.3 – 9.9 years) compared with diabetic recipients (mean: 7.4 years, 95% CI: 6.6 – 8.3 years) as shown below (figure 6.4.3).

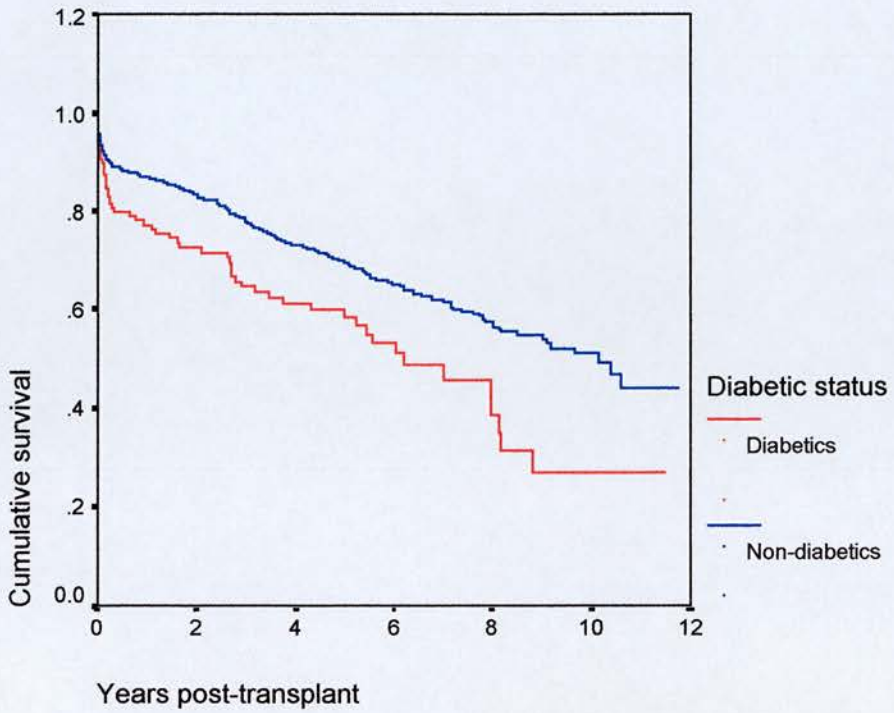


	Non diabetics		Diabetics	
	Number at risk	Survival (%)	Number at risk	Survival (%)
1 year	826	96	108	90
3 years	53	91	73	79
5 years	409	86	48	73
10 years	19	68	5	35

Figure 6.4.3 Patient survival following transplantation according to the diabetic status of the recipient

Only 73% of the diabetic transplant recipients are alive at 5 years compared with 86% of the non-diabetics, while at 10 years the differences are even greater, 35% for the diabetics versus 68% for all other patients.

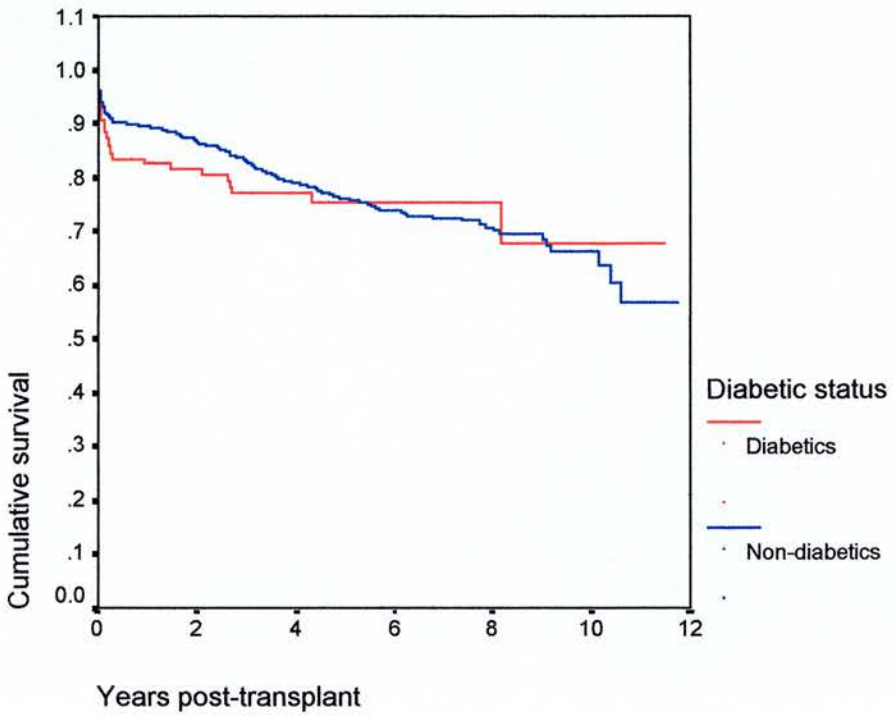
A similar trend is noted for graft survival (figure 6.4.4), with a mean graft survival of 7.8 years (95%CI: 7.4 – 8.2 years) for non-diabetics, compared with a mean of 6 years for the diabetics (95% CI: 5.1 – 6.9 years), (p=0.0004, Log rank test).



	Non diabetics		Diabetics	
	Number at risk	Survival (%)	Number at risk	Survival (%)
1 year	747	87	91	77
3 years	503	78	60	65
5 years	322	70	37	58
10 years	34	51	4	27

Figure 6.4.4 Graft survival according to the diabetic status of the recipient

When graft survival was censored for death with functioning graft, the two survival curves (figure 6.4.5) were comparable (p=0.52, Log rank test), indicating that a large proportion of diabetic transplant recipients die with a functioning graft



	Non diabetics		Diabetics	
	Number at risk	Survival (%)	Number at risk	Survival (%)
1 year	747	90	91	83
3 years	503	83	60	77
5 years	322	76	37	75
10 years	34	66	4	67

Figure 6.4.5 Graft survival, censored for death with functioning graft, according to the diabetic status of the recipient

As the rate of death is higher in the first 12 months post-transplantation, compared with the remaining follow-up period, patient and graft half-life were estimated using the formula shown in figure 6.3.2.

	Non-diabetics n=965	Diabetics n=130	p value
Patient half-life	19.8	9.4	
Adjusted RR of death (95%CI)	1	2.65 (1.83 - 3.85)	<0.0001
Graft half-life	11.8	7.8	
Adjusted RR of graft failure (95%CI)	1	1.68 (1.23 – 2.29)	0.001

Table 6.4.5 Patient and graft half-life and the relative risks of death and graft failure for diabetic transplant recipients compared to all other transplanted patients (Cox regression analysis)

Patient half-life expectancy in a diabetic patient following transplantation is 9 years, half of that for all other transplant recipients. Similarly, the half-life of a kidney graft in a diabetic recipient is 7.8 years, which is 66% of that expected in non-diabetic transplant recipients. The presence of diabetes is a significant risk factor for both patient death and graft loss following transplantation. In a multivariate model adjusted for sociodemographic variables, the presence of diabetes was the strongest factor predicting patient's death and graft loss (table 6.4.5). These results were identical when the analysis was restricted to those patients where the comorbid index

was available and the Cox regression model was adjusted for the presence of these illnesses.

It is important to note that 50% of all grafts lost in the diabetic recipients are due to patient's death, twice as many as in the non-diabetic group. The number of kidneys lost to immunological causes or due to vascular problems is comparable in the two groups of patients, while in a higher proportion of non-diabetic recipients a cause of graft failure could not be ascertained.

Cause of graft failure	**Non-diabetics n=298**	**Diabetics n=58**	**p value**
Death with functioning graft (%)	29.1	50	0.004*
Immunological failures (%)	29.7	20.7	0.208
Vascular problems (%)	9.7	12.1	0.762
Unknown (%)	20.8	12.1	0.174

Table 6.4.6 Causes of graft failure according to the diabetic status of the recipient (χ^2, * - statistical significant)

Although diabetic patients have a significantly higher comorbidity index, there is a similar distribution of the causes of death between the two groups, one in three patients dying due a cardiac problem (table 6.4.7) and almost one quarter without a documented reason for death in either group.

Cause of death	Non-diabetics n=150	Diabetics n=42	p value
Cardiac (%)	30	30.3	0.973
Vascular (%)	13.3	14.3	0.923
Infection (%)	19.3	16.7	0.867
Cancer (%)	7.3	9.5	0.887
Unknown (%)	22.7	23.8	0.958

Table 6.4.7 Causes of patient death according to the diabetic status of the recipient (χ^2)

The results of transplantation in diabetics are inferior to those obtained in all other patients and therefore an important question to answer is whether renal transplantation is the optimum treatment modality for these patients. As pancreatic transplantation is a fairly recent acquisition to the therapeutic armamentarium in Scotland, no direct comparisons were feasible. However, a comparison between survival on dialysis and survival following transplantation could be carried out. This allows diabetic patients to make an informed choice when deciding on the opportunity of listing and transplantation and whether the higher operative and postoperative risks are counterbalanced by significant long-term benefit. To investigate this issue, the risk of death following transplantation at 30 day, between 30 and 365 days and beyond a year was compared with the risk of death on dialysis (table 6.4.8).

Subgroup	*< 30 days*	*31 – 365 days*	*> 365 days*
Diabetic recipients	0.58 (0.08-4.24)	0.56 (0.29-1.10)	0.30 (0.18-0.52)*
Non-diabetic recipients	0.90 (0.33-2.42)	0.72 (0.50-1.03)	0.33 (0.26-0.43)*

Table 6.4.8 The relative risk of death following transplantation at different intervals compared with dialysis for diabetics and non-diabetics (The reference group are all patients on dialysis listed for transplantation) (Time dependant Cox regression analysis adjusted for socio-demographic variables, * = statistical significant, $p< 0.0001$)

Renal transplantation in diabetics does not provide any significant survival benefit over dialysis in the first postoperative year. Beyond a year, however, the risk of dying is 70% lower compared with the risk on dialysis. For comparison, an identical trend was noticed for non-diabetics patients who enjoy a 67% reduction in the risk of death at one year following transplantation. So, renal transplantation in diabetics, although not as successful in prolonging life as in non-diabetics, is clearly a better treatment option compared with dialysis.

6.4.4 Discussion

Diabetes mellitus is the leading cause of renal failure in many countries. As the number of patients with diabetes referred for transplantation is likely to continue to increase, in the current shortage of donor organs, it is important to ascertain the utility of kidney transplantation in diabetic patients relative to other primary renal diseases as well as relative to maintenance dialysis.

In this study, diabetic nephropathy was present in only 16% of all adult patients starting RRT, but the incidence may very well be higher, as comorbidity data was not available for all patients, and therefore only those with diabetes leading to renal failure have been considered.

Patients with diabetic nephropathy are less likely to be listed for transplantation and transplanted compared with non-diabetics. The reduction is largely due to those with type 2 diabetes - only 5% of the patients with this type of diabetes mellitus in the present cohort being transplanted. This may be partly explained by a higher index of comorbidity and poorer transplant results described in these patients (279) and partly by a lack of agreement on the appropriateness of transplanting a kidney in a patient with type 2 diabetes (291).

There is no doubt from the present data that diabetic transplant candidates have a significantly higher comorbidity load compared with non-diabetic patients listed for transplantation. In particular, high-risk factors for patient death and graft loss such as peripheral vascular disease (284), coronary disease (292) and obesity are present in more than 40% of the patients. It is not surprising that with such high comorbidity

these patients have a reduced functional capacity (274;293) and an increased mortality risk (290), both on dialysis as well as after transplantation. A diabetic's risk of dying is three times higher while on the waiting list and twice higher after transplantation compared with non-diabetics patients.

Despite being a high-risk group, diabetic patients are not discriminated against when it comes to transplantation and they receive grafts of similar quality in terms of HLA matching, length of cold ischaemia time or donor age. It can be argued that most of the diabetics in this cohort were type I and hence younger, and in order to provide the best chance of survival, better quality kidneys should be given to them. At the other extreme, there are some who consider that these patients are better served by undergoing long-term dialysis (291) due to the poorer long-term results.

Survival of the diabetic patients is worse than for the non-diabetics on all forms of replacement therapy (31;276). At five and ten years following transplantation, 13% and respectively 33% fewer diabetics are alive compared with non-diabetic recipients.

The survival rates noted in this study are better than most other reported data (table 6.4.9). In addition, this is one of the few investigations to report a 10 year survival rate for diabetic recipients (281;294;295). The discrepancies in the reported survival rates may be explained in part by differences in patient population, pre-transplant assessment and selection methods.

Study	Type of diabetes	Patient survival		Graft survival	
		1 year	5 years	1 year	5 years
Hirschl	I	69	62		
	2	75	58		
Greenfell	I + 2	69	54 (3 yr)		
Gonzalez	I + 2		92 (3 yr)	92	
Rodriguez	I + 2	87	83 (3yr)	70	55 (3yr)
Khauli	I + 2	81	45		
Kim	I		86		71
Carlstrom	I		75		60
Ekstrand	I + 2	82	45 (7 yr)		
Kronson	2		61		53
Kumar	I		76	81	62
Mazucchi	I + 2		89		
Nyberg	2	89	67	81	56

Table 6.4.9 Patient and graft survival in other published series (274;279;281;283;290;292;296-301)

As far as graft survival is concerned, at 5 and 10 years, 12% and respectively 24% fewer grafts were functional in diabetic compared with non-diabetic patients, but as previously noted, graft survival censored for death with functioning graft is comparable between the two groups, as a result of the fact that 50% of the grafts were lost due to patient's death in the diabetic group. There are indications that living donation rather than cadaveric transplantation may be a better solution for patients with diabetic nephropathy (286).

The expected patient and graft life is 50% and respectively 60% shorter in diabetics versus non-diabetics. Although these differences are striking, it is worthwhile noting that most of the remaining life for diabetics is likely to be dialysis free (9.4 years

patient half-life and 7.86 years graft half-life respectively), which will provide at least a better quality of life (24).

The presence of diabetes in a transplant recipient is the most significant factor predicting patient's death (RR=2.65, 95%CI: 1.83-3.85) and the loss of a functioning graft (RR=1.68, 95%CI: 1.23-2.29) in a multivariate analysis. Some (291) use such findings as the main argument for continuing the diabetics on dialysis, but such a line of treatment will deprive these patients of a better treatment option. Our data agree with other studies (19;21;236;300) in observing that the risk of death among diabetics recipients of a kidney transplant is significantly lower compared with diabetic waitlisted patients. In fact, the magnitude of the survival benefit noted here (RR = 0.30) is comparable with that noted in two studies from the US (RR=0.25 (21) and RR=0.27 (19) respectively) that were constructed in a similar manner, using a time-dependant Cox-regression analysis to eliminate the time-to-treatment bias.

Pancreas transplantation has emerged as an important option (302) for the management of patients with type I diabetic nephropathy, but clearly, not all patients will be suitable for such a major procedure (289). Recent progresses in islet transplantation could make this procedure an attractive alternative to whole organ transplantation as it is a simpler and safer procedure, but the exact indications remain to be defined (288). As a well-established pancreas transplant programme has only been started in Scotland in 2000, a proper comparison between the results of simultaneous kidney-pancreas versus kidney alone transplantation was not feasible, but results reported elsewhere seem to indicate that both procedures are equally successful (287;294).

The data available for this study did not allow us to compare the results for the two types of diabetes, as the number of those with type 2 receiving a transplant was small. It is conceivable that the true incidence of type 2 diabetes is higher in Scotland, but the lack of a comprehensive comorbidity data set as well as the possibility of miscoded diagnosis (most of the diabetic patients starting RRT will be on insulin) made such an investigation futile. Nevertheless, data from countries where the incidence of type 2 is much higher seem to indicate that nowadays, comparable success rates are within reach (290).

6.4.5 Conclusion

In conclusion, diabetic nephropathy represents one of the biggest challenges facing transplant activity. With an increased number of comorbid illnesses and a diminished life expectancy, these patients are far from being an ideal candidate, but as many other risk groups, they have an equal right for a chance of transplantation. The lower success rate achieved in these patients should be put into perspective, with consideration given to a longer and a better quality life achieved in transplant recipients compared with dialysis patients.

Summary

These analyses of Scottish data have highlighted a series of important issues for the transplant activity in this country:

1. Centre effect:

Patient assessment is the crucial step in deciding eligibility for transplantation and despite generally acceptable listing criteria, there are wide variation in the clinical practice. These differences may lead to potential bias in access to the service and therefore, there is a clear need for clinical practice guidelines, such as the ones already in place in the USA (18).

2. Elderly patients:

Elderly patients represent the largest and fastest growing group of patients requiring replacement therapy. These patients have a higher comorbidity index and a shorter life span, but transplantation should not be denied on the grounds of age, as it is a feasible and successful undertaking and provides a longer and better quality of life compared to dialysis.

3. **Diabetic patients**:

The incidence of diabetic nephropathy and in particular that associated with type II diabetes is likely to increase in the near future. Although the results of transplantation are not as good as those obtained in other renal diseases, a kidney graft offers the best chance of survival and almost an entirely dialysis-free life expectancy.

CHAPTER 7

A RISK ASSESSMENT SCORE TO PREDICT PATIENT SURVIVAL AT THE MOMENT OF LISTING FOR TRANSPLANTATION

7.1 Introduction

Patients who are referred for transplantation are in general quite knowledgeable about their renal disease and its impact on their life style, as most of them have spent some time on dialysis. The assessment process and subsequent acceptance onto the waiting list opens the gate towards a new and uncharted dimension and patients will have a lot of questions. Some of these questions are relatively easy to answer. There is enough evidence to enable the health professionals to inform patients about how organs are allocated, what happens when a kidney becomes available, how great is the risk of complications, what is the likelihood of a successful transplant. Some questions, such as how long does someone have to wait for a transplant, will be more difficult to answer as there are many factors involved, and some of them, such as availability of donor organs, are beyond the control of the local transplant team.

However, the question – *"How long am I likely to survive?"* – remains difficult to answer. The reasons reside with the complexity of the issue and there are many variables which must be considered. First of all, from the patient's point of view, the presence of certain medical conditions will reduce life expectancy (303-305) (174;186). This would happen in a normal population as well, but under dialysis conditions, some of these illnesses are likely to progress at a faster rate and sometimes the patient may become unsuitable for transplantation or worse, die, before a kidney is available. Secondly, it is quite difficult to estimate when a donor organ will be available and it has been suggested that a longer time spent on dialysis

will negatively impact on survival after transplantation (47). Finally, assuming that a kidney is available, there are numerous other factors – donor's age and cause of death (306), length of cold ischaemic time, degree of HLA matching (96), acute rejection and delayed graft function episodes (307) - that will affect the success rate of a transplant and inevitably patient's survival.

As a large set of data for patients listed for transplantation in Scotland in the last decade was available, we attempted to devise a method of estimating survival from the moment of acceptance to the waiting list. This risk assessment score could be used to help patients in making an informed choice regarding the best treatment option and the likelihood of survival based on their general health status at assessment.

7.2 Survival estimation

1022 adult patients listed for transplantation between 1st of January 1989 and 31st of December 1999 were included in this analysis. Socio-demographic data was collected from the SRR and UKT and extensive comorbidity data was retrieved from case notes, as described in the previous chapters.

Actuarial survival from the time of admission onto the renal transplant waiting list was calculated at 1, 3, 5 and 10 years using a Cox proportional hazards model. The likelihood of survival was predicted based on demographic variables (age, gender, social deprivation, centre of treatment, blood group) and associated medical condition (peripheral vascular disease, ischaemic heart disease, left ventricular hypertrophy, cardiac arrhythmias, diabetes, previous neoplasia, respiratory disease, CVD, smoking status and BMI) present in any given patient when listed.

The treatment modality is time-dependant and therefore at listing, the precise moment when the patient will be transplanted is unknown. To solve this problem, the model was built to predict survival from the listing moment under different scenarios:

1. ***"Average treatment"*** - which predicted survival irrespective of the treatment modality (for this model it was assumed that all patients were going to receive the same kind of treatment, which was unknown at listing).
2. ***"No transplant"*** - in this model it was considered that patients remained on maintenance dialysis. For this particular model, patients were censored once they were transplanted.

3. ***"Post transplant" (Survival with a transplant)*** - assuming that patients were transplanted the following day after listing. This particular estimate may not be of practical use at the time of entry to the waiting list, as it is highly unlikely that a patient will be transplanted the following day after listing. In real terms, patients must be fit enough to survive on average 17 months until transplantation.
4. ***"Transplant 17mo" (Transplant after a median time of 17 months on the waiting list).*** The median waiting time for a kidney transplant in Scotland throughout the follow-up period (1st of January 1989 – 31st of December 2000) was 17 months. For a uniform approach and an easier clinical use, the impact of transplantation after this average waiting time was determined.

In order to identify which factors should be used in the predictive models, a baseline Cox regression analysis was built to determine the socio-demographic and comorbid conditions with a significant impact on survival, under the assumption of an "*average treatment*". The analysis was built in a stepwise manner, which allowed only significant factors to be retained in the final model. A level of significance of 20% was set and all factors with p-values < 0.20 (figure A.4.1, appendix, page 356) were retained for inclusion in all subsequent models.

Three survival models were built: ***"average treatment"***, ***"no transplant"*** and ***"post transplant"*** (figure A.4.2-A.4.4, appendix, page 357-359) and for each predictive variable identified in the baseline model, an estimate of impact on survival under each scenario was determined from the Cox regression (table 7.1).

Predictive variable	Individual estimate		
	"Average treatment"	"No transplant"	"Post transplant"
35-49 years old	0.75389	-0.01494	1.13495
50-59 years old	1.46363	1.00082	1.58291
60-64 years old	1.54045	0.91014	1.99169
>65 years old	2.32296	1.27792	2.75975
Female gender	0.24861	0.00564	0.39573
Transplant centre 2	0.82955	0.64872	1.04668
Transplant centre 3	-0.44666	-1.09392	-0.04090
Diabetes	0.97736	1.35650	0.91256
Ischaemic heart disease	0.34356	0.38346	-0.04642
Hypertension	0.42601	0.11743	0.67537
Valvular disease	0.48013	0.66919	0.43998
Pulmonary embolism	-0.76258	-0.36521	-0.86400
Arrhythmias	0.38039	0.08141	0.14464
Other heart diseases	0.58845	0.44600	0.52389
Cerebrovascular disease	0.41491	0.78555	0.15750
Respiratory disease	0.46732	0.50438	0.34763
GI disorders	0.22936	0.17034	0.31930
Neoplasia	0.73981	0.49526	1.20736
Smoker	0.29710	-0.09141	0.69125
BMI < 20	0.53309	0.36899	0.73837
Blood group A	-0.26312	-0.01486	-0.17645
SUM OF VARIABLES (z)	**Score_ave**	**Score_nt**	**Score_t**

Table 7.1 Predictive variables and individual estimates of impact on survival in three separate models (Cox regression analysis)

According to the Cox regression model (228) survival at a given time point – "***t***" - can be calculated by:

$$\mathbf{S_t(z=0)^{exp(z)}}$$

where "z" is the linear sum of all parameters included in the model:

$$\mathbf{z = \sum_i x_i b_i}$$

where b_i = i^{th} parameter estimate from Cox model

x_i = value of i^{th} parameter (usually 0 or 1 defining the presence or the absence of the factor)

$S_t(z=0)$ is the survival at time **"t"**, for a patient with all predictive variables listed above equal to zero *("baseline survival")*. In other words, in each of the three models, at any given time point, a baseline survival for a patient with none of the factors listed in table 7.1 can be determined. Survival probability for any other patient can be calculated by raising this baseline survival at an exponent, which is the sum of the estimates for all the predictive variables present in that particular patient ("Score_ave", "Score_nt" and "Score_t" respectively).

To estimate survival after transplantation after an average waiting time of 17 months ("transplant_17mo") a more complex approach is necessary. Survival at 1 year is the same as survival at 1 year under the 'no transplantation' scenario. Survival at 3, 5

and 10 years is obtained as the product of the probability that the patient survives to 17 months with no transplant, multiplied by the probabilities that he/she survives a further 19, 53 and 353 months following transplant (all calculated using the formula described). It is expected that survival at 10 years will be less accurate than at 1-5 years because fewer patients had been followed up for this length of time in the prediction models.

The equations obtained to calculate survival under each scenario at 1,3,5 and 10 years are listed in table 7.2.

Clinical scenario	Survival estimate equations
Average treatment	1 year $= 0.99858^{\exp(score\_ave)}$
	3 years $= 0.99447^{\exp(score\_ave)}$
	5 years $= 0.98832^{\exp(score\_ave)}$
	10 years $= 0.96365^{\exp(score\_ave)}$
No Transplant	1 year $= 0.99460^{\exp(score\_nt)}$
	3 years $= 0.96920^{\exp(score\_nt)}$
	5 years $= 0.90946^{\exp(score\_nt)}$
	10 years $= 0.65756^{\exp(score\_nt)}$
Post Transplant	1 year $= 0.99938^{\exp(score\_t)}$
	3 years $= 0.99832^{\exp(score\_t)}$
	5 years $= 0.99717^{\exp(score\_t)}$
	10 years $= 0.98818^{\exp(score\_t)}$
Transplant_17 months	1 year $= 0.99460^{\exp(score\_nt)}$
	3 years $= 0.9874^{\exp(score\_nt)} * 0.99933^{\exp(score\_t)}$
	5 years $= 0.9874^{\exp(score\_nt)} * 0.99809^{\exp(score\_t)}$
	10 years $= 0.9874^{\exp(score\_nt)} * 0.98996^{\exp(score\_t)}$

Table 7.2 Equations used to calculate survival at 1,3,5 and 10 years in each of the prognostic models

To make the use of this score more practical, a spreadsheet was devised. For each new patient, survival is obtained by entering a value of "1" for all factors present with the exception of gender, where a "1" is entered for males and "2" is entered for females. If a field is left missing it is assumed that the factor is absent. Survival predictions will automatically appear in the appropriate columns of the spreadsheet.

7.3 Practical examples

To illustrate how the score can be used in a practical setting, in the assessment clinic, consider the following clinical scenarios and the predictive score for these hypothetical individuals.

a. The "Ideal candidate"

A 28-year-old male is assessed for listing for transplantation in centre 4. He has renal failure due to glomerulonephritis, no associated comorbidity, is a non-smoker, has a normal body mass index (BMI) and is blood group O. This patient has no contraindication to transplantation and therefore is listed. According to this model, this patient will have 66% chances of surviving at ten years if a transplant is not available and 97% probability of being alive at the same time point if a transplant becomes available in 17 months (**Case A**, figure 7.1).

Survival probabilities will be identical for a female patient of similar age and with an identical health status (**Case B**, Figure 7.1).

Case	Centre 2	Centre 3	Gender	35-49 yr	50-59 yr	60-64 yr	>65 yr	Diabetes	Hypertension	IHD	Valvular disease	PE
A	0	0	1	0	0	0	0	0	0	0	0	0
B	0	0	2	0	0	0	0	0	0	0	0	0
C	0	0	2	0	1	0	0	1	1	1	0	0
D	1	0	1	0	0	0	1	1	1	1	0	0
E	1	0	1	1	0	0	0	0	1	0	0	0

Case	Arrhthymias	Other heart disease	Respiratory disease	CVD	Neoplasia	GI disorders	Bl. Grp. A	Malnourished	Smoker
A	0	0	0	0	0	0	0	0	0
B	0	0	0	0	0	0	0	0	0
C	0	0	1	1	0	0	0	0	1
D	0	0	0	1	0	0	1	0	0
E	0	0	1	0	0	1	0	0	1

Case	Average treatment				No transplant			Post-transplant			Transplantation after 17 months			
	1yr	3yr	5yr	10yr	1yr	3yr	5yr	10yr	1yr	3yr	5yr	10yr	1yr	3yr	5yr	10yr
A	1.00	0.99	0.99	0.95	0.99	0.97	0.91	0.66	1.00	1.00	1.00	0.98	0.99	0.99	0.98	0.97
B	1.00	0.99	0.98	0.94	0.99	0.97	0.91	0.65	1.00	1.00	0.99	0.97	0.99	0.99	0.98	0.97
C	0.83	0.48	0.21	0.01	0.73	0.16	0.00	0.00	0.90	0.76	0.62	0.14	0.73	0.43	0.35	0.09
D	0.75	0.33	0.09	0.00	0.60	0.05	0.00	0.00	0.83	0.60	0.42	0.03	0.60	0.24	0.16	0.01
E	0.96	0.87	0.74	0.38	0.98	0.89	0.70	0.20	0.94	0.84	0.75	0.30	0.98	0.89	0.79	0.35

Figure 7.1 Practical examples for the use of the prognostic scores

b. The "high-risk candidate"

A 55-year-old female is assessed for listing for transplantation in centre 1. She has renal failure due to diabetic nephropathy. She is hypertensive and had a myocardial infarction 7 years previously. 5 years prior to the assessment she had a documented cerebrovascular accident from which she made a full recovery. She smokes 2 cigarettes per day and has a degree of emphysema on her chest X-ray. Her body mass index (BMI) is normal and she is blood group AB. After consultation between nephrologists, surgeons and anaesthetists, this patient is listed. According to the model:

a. she will be dead within 5 years without a transplant
b. if a transplant becomes available in 17 months, she will have a 35% and 9% chance of being alive at 5 years and 10 years respectively (**Case C**, figure 7.1).

A 65 year-old diabetic male is referred for assessment at the transplant centre 2. He is hypertensive, has angina of effort, had one episode of transient ischaemic attack and has chronic obstructive airway disease. He has no other associated illnesses, is a non-smoker and his weight is within the normal range for his age and height. After careful consideration, this patient is admitted onto the waiting list. According to the model he has 60% chances of being alive at one year and only 5% probability of living to 3 years. Assuming he survives 17 months and is

transplanted, his long-term survival will be 16% better at 5 years, but he is still likely to die within 10 years (**Case D**, figure 7.1).

c. The "average candidate"

A 40 year-old male with renal failure due to hypertension is assessed for transplantation in centre 1. He has a history of duodenal ulcer and chronic bronchitis and smokes 2-3 cigarettes per day. He has no major contraindication to transplantation and is listed. His survival probability without transplantation is good, with a 70% chance of being alive at 5 years and 20% chance of living beyond 10 years. In his case, after transplantation, the prognosis is poorer in the first years, but on long-term, there is a 15% better chance of surviving at 10 years (**Case E**, figure 7.1).

7.4 Discussion

Kidney transplantation is well accepted nowadays as the best form of treatment for patients with end-stage renal failure as it provides a better and a significantly longer life (19). The majority of patients are aware of these advantages and not surprisingly, most of their questions at assessment and listing for transplantation surround the issues of access to a kidney graft and survival benefit. Although a better survival has been demonstrated in large population-based studies, to try and estimate individual patient survival is a more complex matter. There are numerous factors that will determine survival and some of them, such as availability of a donor organ, are impossible to predict at the moment of listing.

In this study we describe for the first time, a survival estimate for individual patients, derived from a large population sample of adult patients listed for transplantation in Scotland in the last decade. These estimates are based on socio-demographic criteria and patient's general health status data, which are readily available at the moment of listing. As treatment modality is itself a time-dependant variable (21), it would be quite difficult to predict when transplantation will occur and how it will affect survival in each patient. To resolve this issue, survival was estimated under three different scenarios that cover all clinical possibilities (no transplant, following a transplant, average treatment and following a transplant which is received 17 months after listing). The 17 months figure was considered for the latter model, as it represents the median waiting time to a kidney transplant in Scotland, as determined from the study cohort.

This prognostic score could provide a useful clinical tool, which can be easily applied in the assessment clinic to estimate a patient's survival, as illustrated by the practical examples given above. Although some of the cases presented seem unlikely to be listed, they are in fact very similar to real-life patients that have been listed and transplanted throughout the duration of this study. The use of a prognostic score, like the one proposed here, will enable clinicians to recommend whether transplantation or dialysis is the best form of treatment for a particular patient, based on health status and estimated survival probability. As shown in some cases, prognosis may be poorer after transplantation, particularly in the early years, and this may influence the choice of therapy. Patients will be able to make an informed decision regarding the benefits and the risks associated with either form of treatment and choose the course of therapy deemed suitable to them.

The idea of a prognostic score is not new and there is no right or wrong model. The advantages of the model presented here are that it takes into account a large number of comorbid conditions – and hence provides a better clinical picture of the recipient – and allows an instant estimate of survival without being too cumbersome to use.

One of the potential drawbacks of the model presented here is that it was derived based on retrospective data which was available only for about 60% of all patients listed during the study period. Therefore, this score needs to be validated prospectively, and with the ever changing demographics of the waiting list population it may well be the case that some of the variables considered will see an alteration of their individual predictive power.

7.5 Conclusion

In summary, based on the best data currently available in Scotland, these prognostic models allow, for the first time, an estimation of survival for patients listed for transplantation, providing a useful clinical and research tool. The advent of such a score is a step forward towards an evidence-based and truly informed choice of replacement therapy for the end-stage renal failure patients.

SUMMARY

As everywhere else in the world, transplantation in Scotland has seen an incredible advance in the last three decades, making it one of the fastest growing fields of medicine. This progress has established transplantation as the preferred choice of treatment for patients with end stage renal failure disease, but the current logistic constraints and in particular, the lack of donor organs, seriously jeopardize any further developments of the service. The current climate of transplantation has raised yet again serious concerns regarding issues such as organ allocation, equity of access, standards of the assessment process and appropriateness of transplantation in certain groups of patients.

As there were virtually no data on these issues in Scotland, and indeed very little elsewhere in the United Kingdom, this thesis had as the first aim to correlate the information available and to provide a longitudinal perspective for end-stage renal failure patients from the moment they start renal replacement therapy and following onto listing for transplantation, transplantation and beyond. Scotland has the unique privilege of having an extensive database for all renal failure patients on dialysis, in the form of the Scottish Renal Registry (SRR), while transplant and post-transplant data for all kidney recipients is collected and stored at the UK Transplant. In addition, case notes can provide the clinical data, which is not stored in either of the two databases. Despite these extensive sources of information, an actual link between them has never been established until the present work. Creating this link, the aims of the thesis were to address the issues outlined above and to answer the questions set out at the end of the first chapter:

1. What are the benefits of the current allocation schemes and the influence of the new regional Scotland–Northern Ireland Alliance on the transplant activity?
2. Is there equity of access to the transplantation service? If not, which are the sociodemographic and comorbidity factors which may be responsible for these differences?
3. Does transplantation provide a survival advantage over dialysis in various renal failure subpopulations? Is there any benefit in transplanting high-risk groups of patients?
4. Are there any differences in the assessment process? Can the risk factors identified at the assessment process be quantified into a patient survival risk score?

Each of the questions will be answered individually on the basis of the information gained during these studies.

1. What are the benefits of the current allocation schemes and the influence of the new regional Scotland–Northern Ireland Alliance on the transplant activity?

The impact of this new alliance was examined in Chapter 2. As the analysis clearly demonstrated, this regional level of organ sharing had significant benefits. There was a substantial improvement in the level of HLA matching, 79% of the transplants

performed in the Alliance being very well matched (Tier 1 or Tier 2) compared with only 64% across the UK. The improvement in HLA matching was sustained over the two-year period of the study, whilst very little improvement was noted for the rest of the UK after the first year of the new allocation scheme. Furthermore, the higher degree of matching was achieved through an increased organ exchange, only 23% of the kidneys being retained locally by the retrieving centre. These improvements were reflected in the structure of the waiting list, with a reduction in the proportion of the long waiting patients, highly sensitised patients and re-transplants. This study has shown that an increased regional organ exchange has no detrimental effect on the length of the cold ischaemic time or graft survival. However, there was a persistent disproportion in kidney distribution amongst the participating centres, a large centre being a net kidney importer.

Further monitoring and computer modelling are required to ensure that the benefits of the alliance are persistent and the balance of exchange is corrected.

2. Is there equity of access to the transplantation service? If not, which are the sociodemographic and comorbidity factors which may be responsible for these differences?

The study performed in Chapter 3 indicated that there were significant differences in access to the transplantation service in Scotland over a period of 11 years. Access to the renal transplant waiting list was found to be dependant on a variety of sociodemographic factors, elderly patients, females, patients with a higher

deprivation score, patients starting RRT on haemodialysis, patients with diabetes and patients living closer to the transplant centre having fewer chances of being admitted onto the waiting list. In addition, there was a significant centre effect, the analyses described in chapter 3 indicating that patients starting dialysis in a renal centre which is in the same hospital as a transplant unit, were more likely to be listed. Once a patient was listed, age, the primary renal disease and the transplant centre remained the only factors with a significant impact on the access to a kidney graft. It is important to note that these findings are not random and they are consistent with the inequities of access noted in the USA (143).

Comorbidity may account for the differences noted in Chapter 3. However, the difficulties in considering the associated medical conditions have long been acknowledged and this is reflected by the paucity of studies incorporating comorbidity in a predictive model of access to transplantation (130;131). The study presented in Chapter 4 overcame some of these difficulties and investigated the impact of comorbidity on the access to the renal transplant waiting list and renal transplantation in Scotland. The presence of left ventricular hypertrophy, cerebro-vascular disease, respiratory disease and previous neoplasia had a negative impact on the likelihood of listing. However, it is important to note that although the addition of comorbid conditions to the model of access to the waiting list presented in Chapter 3 improved the predictive power of the model, it did not diminish the level of significance of the individual socio-demographic variables. In contrast, there were significant changes in the predictive value of the socio-demographic variables when the model of access to transplantation was corrected for comorbidity. After adjustment for comorbidity, the primary renal disease and age lost their impact on

the likelihood of transplantation, suggesting that their effect could have been due entirely to an unequal comorbidity load across different age groups or causes of renal failure.

The findings presented in Chapter 3 and 4 suggest that the differences in access to the waiting list and transplantation noted for different socio-demographic variables cannot be explained entirely by the presence of the comorbid conditions. Secondly, these studies indicate that the prevalence of the comorbid conditions is worse among patients on dialysis compared with kidney transplant recipients. With a significantly higher number of factors determining the access to the renal waiting list it is clear that the main obstacle on the pathway to transplantation is at the listing stage rather than at transplantation once on the waiting list.

Further prospective investigations into the reasons behind some of these differences as well as a comprehensive database containing socio-demographic and comorbidity data may identify the changes in the demographics of the RRT population and help correcting the inequities in access to the service noted in these studies.

3. Does transplantation provide a survival advantage over dialysis in various renal failure subpopulations? Is there any benefit in transplanting high-risk groups of patients?

The study performed in Chapter 5 identified a substantial long-term survival advantage for transplantation compared with dialysis in patients considered suitable candidates for renal transplantation. Transplant recipients appeared to have a higher

immediate postoperative (30 days) mortality compared with mortality on continued dialysis, this finding being even more obvious when survival was censored for graft failure. However, beyond a year, transplant recipients have a significantly lower risk of death, which leads to a substantially longer life expectancy compared with patients on dialysis on the waiting list. As shown by the results of chapter 5, this effect seems to be intrinsic to the treatment itself rather than an effect of patient selection or higher dialysis mortality. As expected, the outcome varies among different kidney transplant recipients, but the survival advantage conferred by transplantation is present is all subgroups of patients, including high-risk ones.

This issue was further investigated in Chapter 6. The results presented in this chapter have shown that elderly patients enjoy a significant benefit from being transplanted rather than continuing on dialysis. Furthermore, despite a higher index of comorbidity in elderly patients on renal replacement therapy, transplantation seems to be a safe and feasible undertaking in these patients and provides a dialysis-free and good quality of remaining life.

The issue of renal transplantation in patients with diabetes mellitus was explored in Chapter 6. This analysis found that diabetic patients have an increased number of comorbid illnesses and a diminished life expectancy and are far from being an ideal candidate for renal transplantation. Although the results are inferior to those obtained in non-diabetic patients, this study has clearly shown that transplantation provides a substantial long-term benefit compared with dialysis and should be the preferred method of treatment whenever possible.

4. Are there any differences in the assessment process? Can the risk factors identified at the assessment process be quantified into a patient survival risk score?

The initial analysis described in Chapter 6 confirmed that there are significant differences in the practice of assessing and listing patients for renal transplantation across Scotland. The study has shown wide variations with regards to factors such as the primary renal disease, age, gender, type of first renal replacement therapy and social deprivation between the four transplant centres. The comorbidity index is a significant factor, different weight being given in each of the four centres to factors such as peripheral vascular disease, ischaemic heart disease, obesity and hyperlipidaemia, which are strongly correlated with an increased risk of death following transplantation.

These findings confirmed previously documented differences in patient selection (199) and highlighted again the need for a consensus and clinical guidelines on assessment for transplantation such as those published by the American Society of Transplantation and the European Dialysis and Transplant Association (157;308).

A variety of socio-demographic (age, gender, transplant centre) and comorbidity factors (cardiovascular disease, respiratory disease, cerebro-vascular disease, neoplasia, gastro-intestinal disorders) have a significant impact on survival. Using these factors, in the analysis in Chapter 7, a complex statistical model was built, to estimate the likelihood of survival from the moment the patient is admitted onto the waiting list, under different clinical scenarios. As the precise moment of transplantation is unpredictable, this risk assessment score presents the patients with

the probability of survival continuing dialysis, receiving a transplant the day after listing, or under the assumption of transplantation after the average waiting time for a kidney graft in Scotland. This score is "user-friendly" and could provide a useful clinical tool to enable patients to make an informed decision regarding the risk and benefits associated with either form of treatment.

With respect to the questions set out at the end of Chapter 1, the following conclusion can be made:

1. There is a significant improvement in the HLA matching, with increased organ sharing, similar cold ischaemic time and graft survival in a wider regional kidney sharing alliance.

2. At present in Scotland there are significant inequalities in access to the transplantation service, which cannot be entirely explained by the presence of comorbidity.

3. Transplantation provides a significant reduction in the long-term risk of death and a substantial increase in the life expectancy compared with dialysis. This benefit is present at different magnitude in all patients considered suitable for transplantation.
4. Currently in Scotland, there is no consensus regarding the assessment and listing for renal transplantation. Based on individual socio-demographics and

comorbidity, a prognosis of the likelihood of survival can be made, to allow patients to make an informed choice of treatment.

In addition to these findings, the work in this thesis has established a novel link between the Scottish Renal Registry and United Kingdom Transplant and clinical data, providing a longitudinal picture of the transplant patients. This thesis has identified a core set of clinical data which has a significant impact on the outcome of the transplant recipient and which could be included in a future prospective comprehensive database. With the rapid changing demographics of the renal replacement population and with the increased ability to treat more complex cases, the advent of such complex data will allow rapid analysis of all the issues described in this thesis and computer modelling of potential solutions.

The work presented in this thesis has highlighted some of the controversial issues confronting the transplant services in Scotland at the dawn of the third millennium and hopefully has helped to provide some answers.

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APPENDIX

Year of transplant	No. at risk at day 0	% survival	95% CI
1989-1992	367	89	86-92
1993-1995	358	92	89-95
1996-1998	480	95	93-97

Table A.1 One year transplant survival after living donor kidney in UK, by year of transplant (*Source: UK Transplant Activity report 2000)*

		1 year		3 years		5 years	
Type of survival	**Year of graft**	**% survival**	**95% CI**	**% survival**	**95% CI**	**% survival**	**95% CI**
Transplant	1990-1992	82	80-84	74	72-76	66	64-68
	1993-1995	83	82-85	76	74-77		
	1996-1997	85	83-86				
Graft	1990-1992	86	85-88	81	79-83	76	74-77
	1993-1995	87	86-88	82	80-83		
	1996-1997	88	86-90				
Patient	1990-1992	95	94-96	91	90-93	87	85-88
	1993-1995	96	95-96	92	91-94		
	1996-1997	96	95-97				

Table A.2 One, three and five year transplant, graft and patient survival after first adult cadaveric kidney transplant in UK 1990-1997, by year of graft (*Source: UK Transplant: Renal Transplant Audit 1990-1998)*

Graft type	Survival interval	Year of grafting										
		1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994
Cadaveric	5 years	42.5	44.5	44.4	46.1	53.0	56.3	57.2	59.1	58.0	58.5	59.1
	10 years	25.3	25.8	26.6	28.4	33.3	35.4					
Living donor	5 years	67.8	71.1	73.6	72.5	70.3	73.7	72.1	74.3	71.5	70.0	71.8
	10 years	49.8	49.9	52.1	50.3	51.3	54.5					

Table A.3 Five and ten year graft survival for cadaveric and living donor transplants in USA (*Adapted from "The 2001 USRDS Annual Data Report Atlas")*

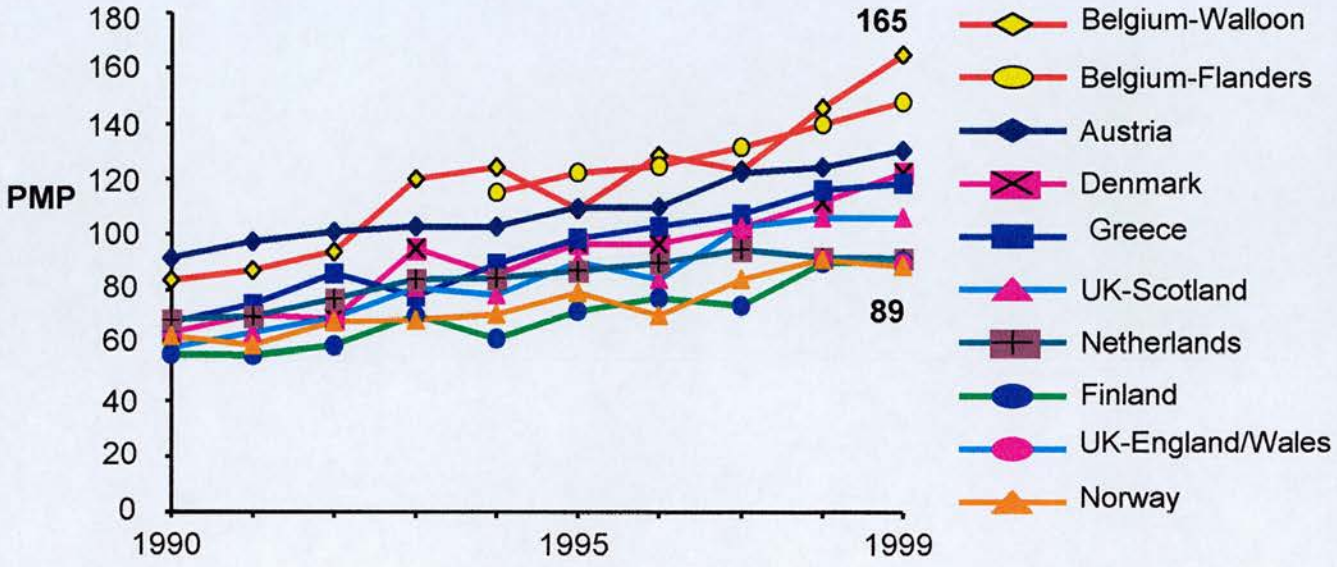

Figure A.1 Crude incidence of RRT 1990-1999, by country (*Source: ERA-EDTA Registry)*

	1990	*1991*	*1992*	*1993*	*1994*	*1995*	*1996*	*1997*	*1998*	*1999*
Rate pmp	190	210	226	232	266	266	276	297	310	317

Table A.4 Change in incident rates of ESRD in USA, 1990 – 1999 (*Source: USRDS)*

No. of alleles	Antigen	No. of alleles	Antigen
HLA-A		3	B53
4	A1	1	B54(22)
32	A2	7	B55(22)
6	A3	5	B56(22)
5	A11	5	B57(17)
1	A23(9)	2	B58(17)
21	A24(9)	1	B59
2	A25(10)	3	B60(40)
12	A26(10)	4	B61(40)
4	A29(19)	15	B62(15)
7	A30(19)	2	B63(15)
4	A31(19)	1	B64(14)
3	A32(19)	1	B65(14)
3	A33(19)	2	B67
2	A34(10)	1	B70
1	A36	2	B71(70)
1	A43	2	B72(70)
3	A66(10)	1	B73
10	A68(28)	5	B75(15)
1	A69(28)	3	B76(15)
3	A74(19)	1	B77(15)
1	A80	4	B78
HLA-B		1	B81
14	B7	1	B82
6	B8	**HLA-DR**	
4	B13	6	DR1
17	B15	3	DR2
7	B18	10	DR3
16	B27	35	DR4
28	B35	2	DR6
2	B37	3	DR7
4	B38(16)	26	DR8
19	B39(16)	1	DR9
13	B40	1	DR10
3	B41	39	DR11(5)
2	B42	8	DR12(5)
11	B44(12)	36	DR13(6)
3	B45(12)	33	DR14(6)
1	B46	10	DR15(2)
3	B47	8	DR16(2)
5	B48	3	DR17(3)
1	B49(12)	2	DR18(3)
1	B50(21)	14	DR51
17	B51(5)	19	DR52
3	B52(5)	10	DR53

Table A.5 Recognized human leukocyte antigen (HLA) specificities (adapted from Bodmer J.G. *et.al.* Nomenclature for factors of the HLA system, 1999. *Hum Immunol* 1999;60:361-395)

CREG	HLA
A01C	A1, A3, A11, A29,A30, A31, A36, A80
A10C	A10, A11, A19, A25, A26, A32, A33, A34, A43, A66, A74
A02C	A2, A9, A23, A24, A28, A68, A69, A203, A210, A2403, B17, B57, B58
B05C	B5, B15, B17, B18, B21, B35, B46, B49, B50, B51, B52, B53, B57, B58, B62, B63, B70, B71, B72, B73, B75, B76, B77, B78, B4005, B5102, B5103
B07C	B7, B13, B22, B27, B40, B41, B42, B47, B48, B54, B55, B56, B59, B60, B61, B67, B81, B8201, B703
B08C	B8, B14, B16, B18, B38, B59, B64, B65, B67, B3901, B3902
B12C	B12, B13, B21, B37, B40, B41, B44, B45, B47, B49, B50, B60, B61, B4005
BW4	B5, B13, B17, B27, B37, B38, B44, B47, B49, B51, B52, B53, B57, B58, B59, B63, B77, B5102, B5103
BW6	B7, B8, B14, B18, B22, B39, B40, B41, B42, B45, B48, B50, B54, B55, B56, B60, B61, B62, B64, B65, B67, B70, B71, B72, B73, B75, B76, B78, B81, B8201, B703, B3901, B3902, B4005

Table A.6 Cross-reactive groups and component antigens

Centre	*Number kidneys identified*	*Population (millions)*	*Number of donors (pmp)*	*Number of transplants performed (pmp)*
Aberdeen	28	0.71	14 (19.7)	11 (14)
Edinburgh	26	1.2	13 (10.8)	27 (22.5)
Glasgow	68	2.7	34 (12.6)	69 (25.5)
Belfast	50	1.6	25 (15.6)	37 (23.1)
Dundee	8	0.4	4 (10)	14 (35)
Total	**180**	**6.61**	**90 (13.6)**	**158 (23.9)**

Table A.7.a Pre-alliance year (1.09.1997 – 31.08.1998)

Centre	*Number kidneys identified*	*Population (millions)*	*Number of donors (pmp)*	*Number of transplants performed (pmp)*
Aberdeen	38	0.71	19 (26.7)	16 (22.5)
Edinburgh	34	1.2	17 (14.1)	34 (28.3)
Glasgow	55	2.7	28 (10.3)	66 (24.4)
Belfast	46	1.6	23 (14.3)	39 (24.3)
Dundee	10	0.4	5 (12.5)	9 (22.5)
Total	**183**	**6.61**	**92 (13.9)**	**164 (24.8)**

Table A.7.b Year 1 (1.09.1998 – 31.08.1999)

Centre	*Number kidneys identified*	*Population (millions)*	*Number of donors (pmp)*	*Number of transplants performed (pmp)*
Aberdeen	14	0.71	7 (9.86)	25 (35.2)
Edinburgh	54	1.2	27 (22.5)	35 (21.8)*
Glasgow	58	2.7	29 (10.7)	92 (34)
Belfast	36	1.6	19 (11.8)	34 (21.2)
Dundee	5	0.4	3 (7.5)	0
Total	**167**	**6.61**	**85 (12.8)**	**186 (28.1)**

Table A.7.c Year 2 (1.09.1999 – 31.08.2000) (*, Dundee merged with Edinburgh, pmp rate calculated for 1.6 million people)

Table A.7.a-c Retrieval activity, total population (millions), number of donors per million population and number of transplants performed for each centre in the pre-alliance year and the first two years of the alliance.

Centre	*Total retrieved*	*Retained retrieving centre (%)*	*Export UKT (%)*	*Export Alliance (%)*
Edinburgh	24	7 (29.1)	9 (37.5)	8 (33.4)
Aberdeen	27	5 (18.5)	8 (29.6)	14 (51.8)
Glasgow	65	44 (67.7)	20 (30.8)	1 (1.5)
Belfast	47	21 (44.7)	22 (46.8)	4 (8.51)
Dundee	8	0	5 (62.5)	3 (37.5)
Total	**171**	**77 (45)**	**64 (37.5)**	**30 (17.5)**

Table A.8.a Pre-alliance year (1.09.1997 – 31.08.1998)

Centre	*Total retrieved*	*Retained retrieving centre (%)*	*Export UKT (%)*	*Export Alliance (%)*
Edinburgh	34	5 (14.7)	13 (38.2)	16 (47)
Aberdeen	34	1 (2.9)	14 (41.2)	19 (55.9)
Glasgow	48	17 (35.4)	19 (39.6)	12 (25)
Belfast	45	11 (24.4)	15 (33.3)	19 (42.2)
Dundee	10	2 (20)	5 (50)	3 (30)
Total	**171**	**36 (21)**	**66 (38.6)**	**69 (40.4)**

Table A.8.b Year 1 (1.09.1998 – 31.08.1999)

Centre	*Total retrieved*	*Retained retrieving centre (%)*	*Export UKT (%)*	*Export Alliance (%)*
Edinburgh	52	9 (17.3)	15 (28.8)	28 (53.8)
Aberdeen	12	1 (8.33)	5 (41.6)	6 (50)
Glasgow	56	25 (44.6)	13 (23.2)	18 (32.1)
Belfast	35	2 (5.7)	15 (42.8)	18 (51.4)
Dundee	5	0	1 (20)	4 (80)
Total	**160**	**37 (23.1)**	**49 (30.6)**	**74 (46.3)**

Table A.8.c Year 2 (1.09.1999 – 31.08.2000)

Table A.8.a-c Destination of kidneys retrieved by each centre and the alliance in each year

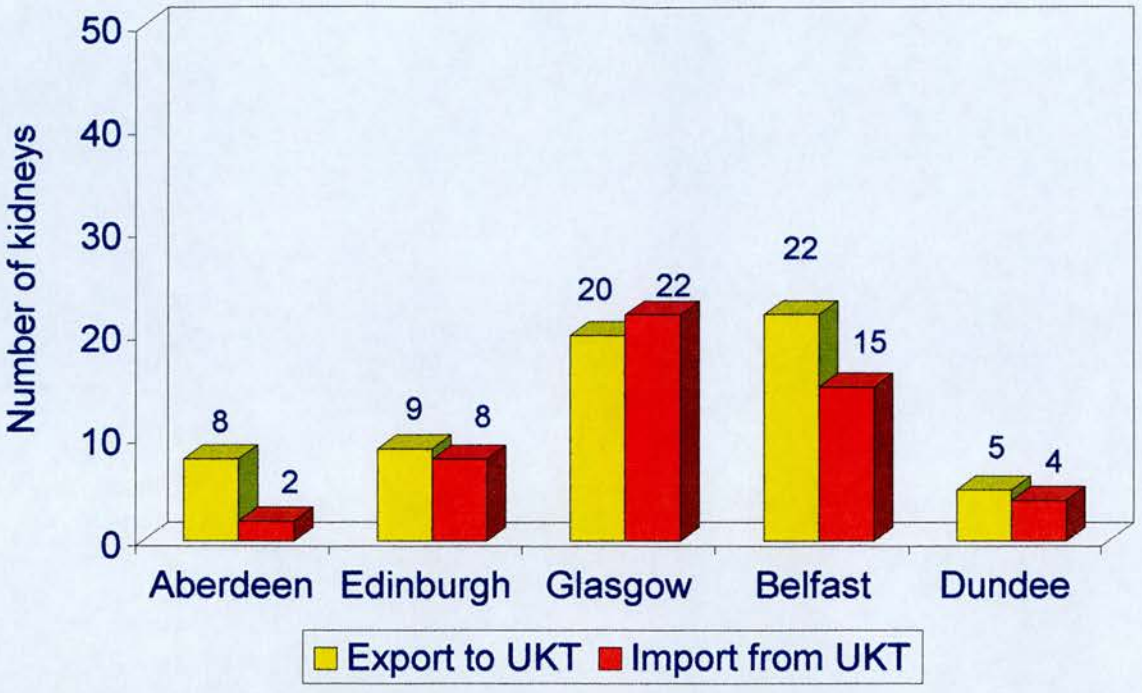

Figure A.2.a Individual centre balance of exchange with UKT in the pre-alliance year (1.09.1997 – 31.08.1998)

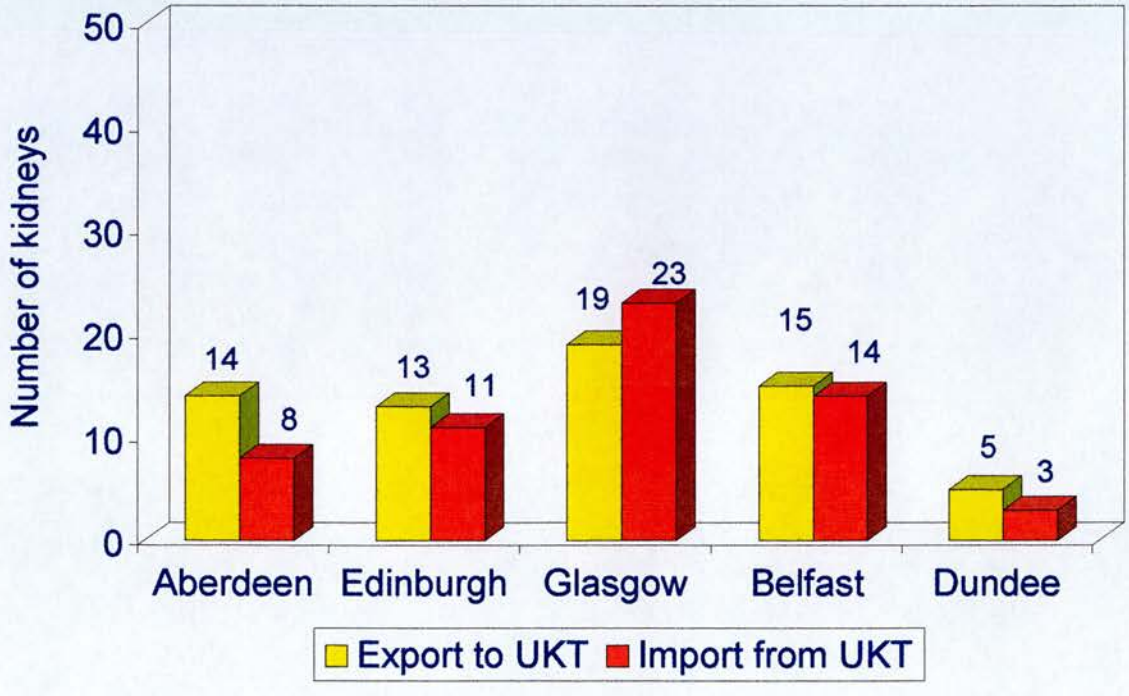

Figure A.2.b Individual centre balance of exchange with UKT in the first alliance year (1.09.1998 – 31.08.1999)

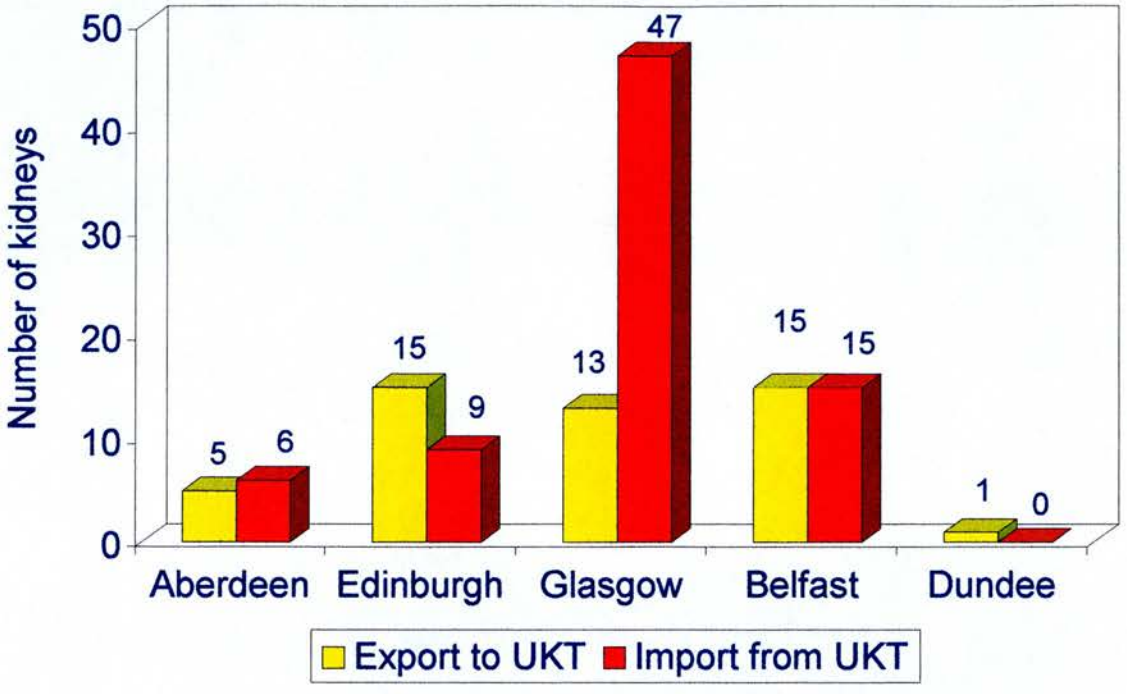

Figure A.2.c Individual centre balance of exchange with UKT in the second alliance year (1.09.1999 – 31.08.2000)

Import from / Export to	Aberdeen	Edinburgh	Glasgow	Belfast	Dundee	*Total imports*
Aberdeen		3	1	1		*4*
Edinburgh	8				3	*12*
Glasgow		1		2		*3*
Belfast		1				*1*
Dundee	6	3		1		*10*
Total exports	*14*	*8*	*1*	*4*	*3*	30
Balance of exchange	**+10**	**-4**	**-2**	**+3**	**-7**	

Table A.9.a Pre-alliance year (1.09.1997 – 31.08.1998)

Import from / Export to	Aberdeen	Edinburgh	Glasgow	Belfast	Dundee	*Total imports*
Aberdeen		2	3	2		*7*
Edinburgh	8		4	6	3	*18*
Glasgow	6	8		10	2	*26*
Belfast	5	4	4		1	*14*
Dundee		2	1	1		*4*
Total exports	*19*	*16*	*12*	*19*	*3*	69
Balance of exchange	**+11**	**+2**	**-14**	**+5**	**-1**	

Table A.9.b Year 1 (1.09.1998 – 31.08.1999)

Import from / Export to	Aberdeen	Edinburgh	Glasgow	Belfast	Dundee	*Total imports*
Aberdeen		5	5	6	2	*18*
Edinburgh	4		7	8		*19*
Glasgow	1	13		4	2	*20*
Belfast	1	10	6			*17*
Dundee						
Total exports	*6*	*28*	*18*	*18*	*4*	74
Balance of exchange	**-12**	**+9**	**-2**	**+1**	**+4**	

Table A.9.c Year 2 (1.09.1999 – 31.08.2000)

Table A.9.a-c Internal balance of exchange of the alliance for each of the three year period

Centre	*Number of kidneys offered*	*Number of kidney accepted*	*Number of kidneys accepted and not used (%)*
Aberdeen	10	6	2 (33.3)
Edinburgh	20	16	4 (25)
Glasgow	15	10	7 (70)
Belfast	8	5	4 (80)
Dundee	20	12	2 (17)
Total	73	49	19 (38.78)

Table A.10.a Pre-alliance year (1.09.1997 – 31.08.1998)

Centre	*Number of kidneys offered*	*Number of kidneys accepted*	*Number of kidneys accepted and not used (%)*
Aberdeen	29	8	1 (12.5)
Edinburgh	27	18	1 (6)
Glasgow	63	43	17 (39.6)
Belfast	52	26	12 (46.2)
Dundee	26	8	3 (37.5)
Total	197	103	34 (33)

Table A.10.b Year 1 (1.09.1998 – 31.08.1999)

Centre	*Number of kidneys offered*	*Number of kidneys accepted*	*Number of kidneys accepted and not used (%)*
Aberdeen	50	21	3 (14.3)
Edinburgh	43	21	2 (9.5)
Glasgow	38	30	10 (33.3)
Belfast	85	25	8 (32)
Dundee	6		
Total	222	97	23 (23.7)

Table A.10.c Year 2 (1.09.1999 – 31.08.2000)

Table A.10.a-c Internal offers made, accepted and accepted and not used by each centre for each of the three year period

Centre	*Kidneys accepted and not used*	*Positive crossmatch*	*Positive crossmatch (%)*
Aberdeen	2	0	0
Edinburgh	4	3	75
Glasgow	7	4	57
Belfast	4	4	100
Dundee	2	1	50
Total	19	12	63

Table A.11.a Pre-alliance year (1.09.1997 – 31.08.1998)

Centre	*Kidneys accepted and not used*	*Positive crossmatch*	*Positive crossmatch (%)*
Aberdeen	1	1	100
Edinburgh	1	1	100
Glasgow	17	12	70
Belfast	12	8	66
Dundee	3	1	33
Total	34	23	52

Table A.11.b Year 1 (1.09.1998 – 31.08.1999)

Centre	*Kidneys accepted and not used*	*Positive crossmatch*	*Positive crossmatch (%)*
Aberdeen	3	1	33
Edinburgh	2	1	50
Glasgow	10	6	60
Belfast	8	6	75
Dundee			
Total	23	14	61

Table A.11.c Year 2 (1.09.1999 – 31.08.2000)

Table A.11.a-c Kidneys accepted and not implanted due to positive crossmatching at the receiving centre in each of the three year period

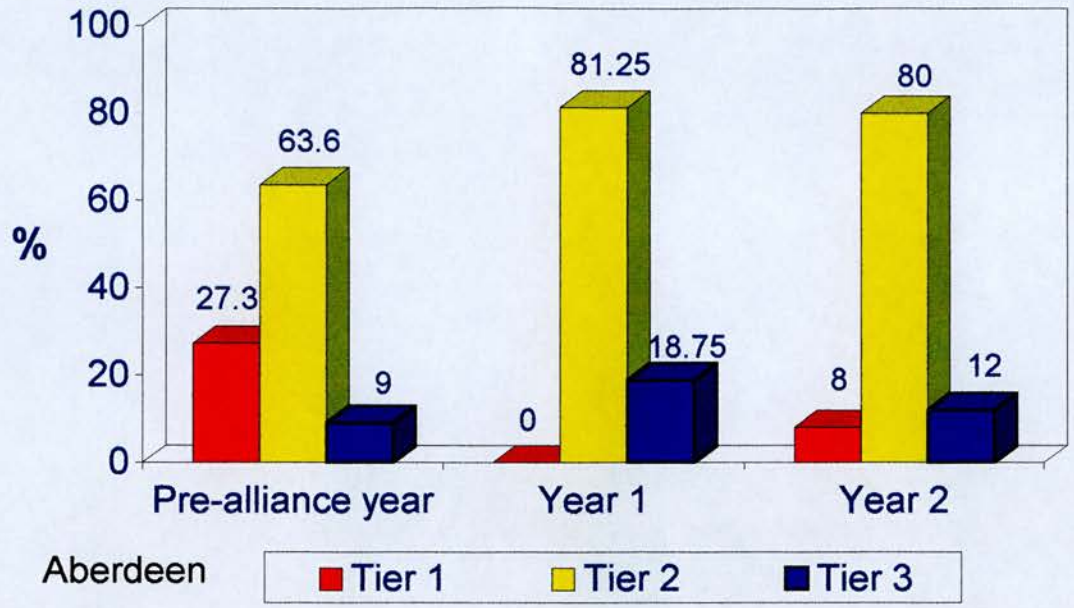

Figure A.3.a % HLA matching for transplants performed in Aberdeen in each year of activity

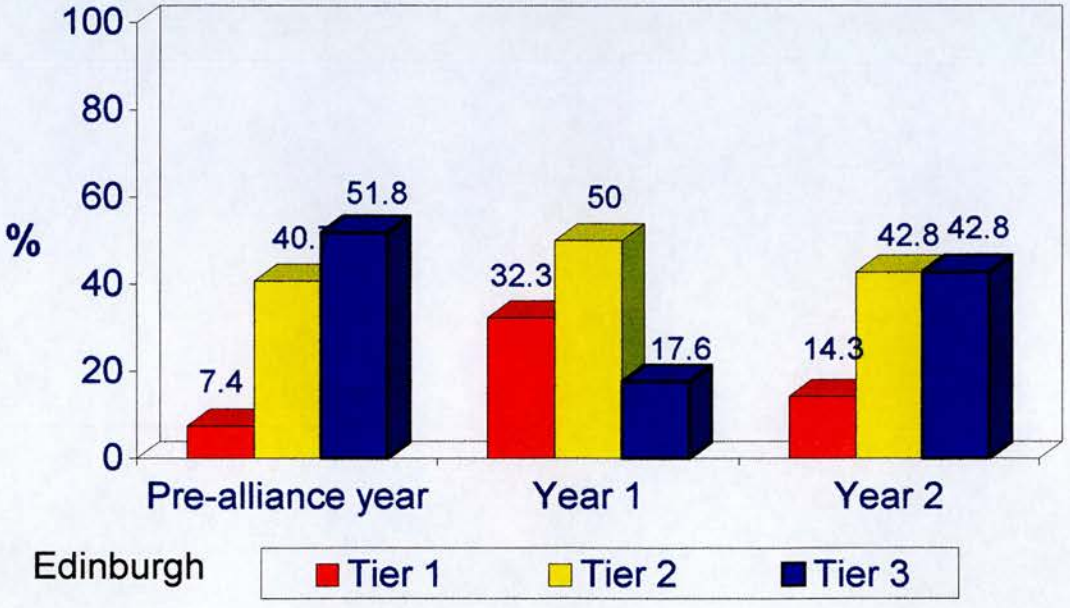

Figure A.3.b % HLA matching for transplants performed in Edinburgh in each year of activity

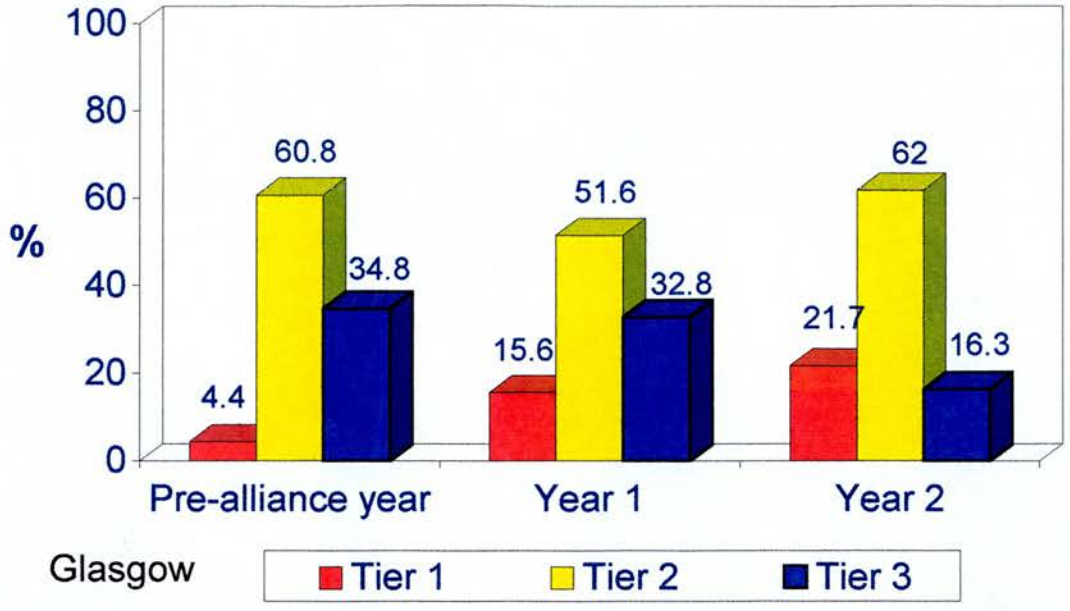

Figure A.3.c % HLA matching for transplants performed in Glasgow in each year of activity

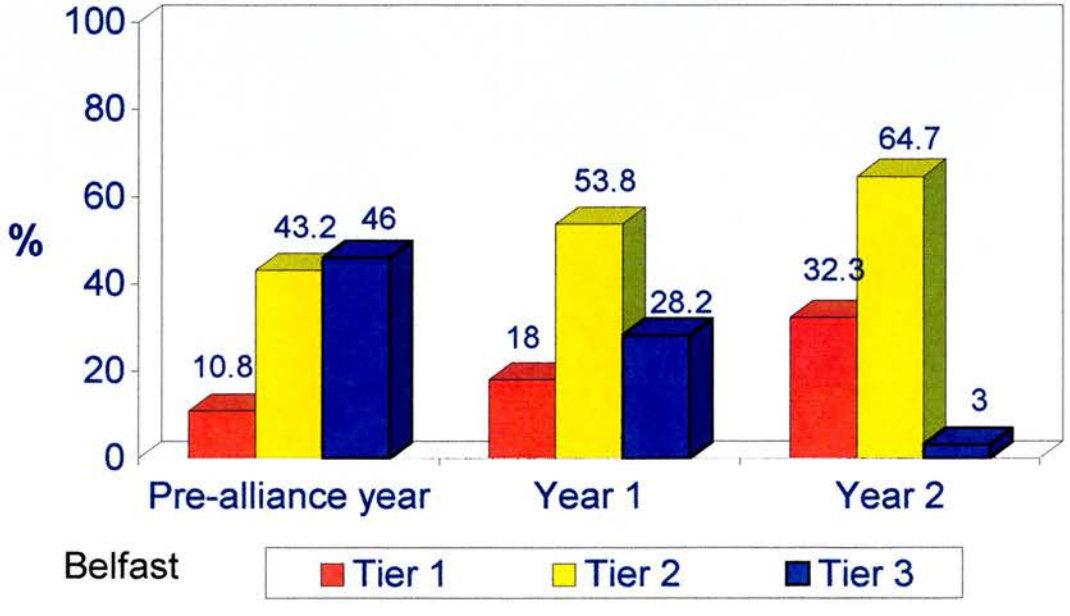

Figure A.3.d % HLA matching for transplants performed in Belfast in each year of activity

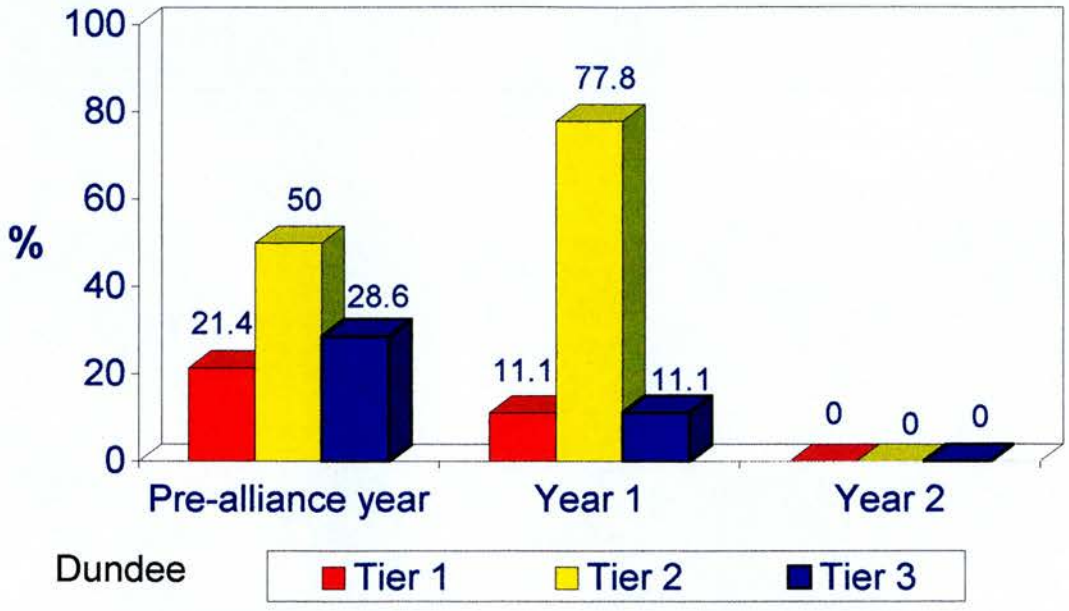

Figure A.3.e % HLA matching for transplants performed in Dundee in each year of activity

Period	Number transplants in analysis	% survival	95% confidence interval
Pre-alliance	15	86.7	69.5 – 100.0
Post-alliance	63	88.9	81.1 – 96.7

Table A.12.a One year graft survival for Tier 1 transplants in the pre- and post-alliance periods (p = 0.7760, Log-Rank test)

Period	Number transplants in analysis	% survival	95% confidence interval
Pre-alliance	83	79.5	70.8 – 88.2
Post-alliance	196	85.4	80.2 – 90.7

Table A.12.b One year graft survival for Tier 2 transplants in the pre- and post-alliance periods (p = 0.2377, Log-Rank test)

Period	Number transplants in analysis	% survival	95% confidence interval
Pre-alliance	59	83.0	73.5 – 92.6
Post-alliance	72	93.8	87.8 – 99.7

Table A.12.c One year graft survival for Tier 3 transplants in the pre- and post-alliance periods (p = 0.0532, Log-Rank test)

Table A.12.a-c One year graft survival for all transplants in the pre- and post-alliance periods, according to the HLA matching tier

Variable	Postcode	$\bar{x}_i$	SD_i
Overcrowding	V_1	X_1	SD_1
Male unemployment	V_2	X_2	SD_2
Low social class	V_3	X_3	SD_3
No car	V_4	X_4	SD_4

Deprivation score $= \sum_{i}^{n=4} (V_i - X_i)/SD_i$

V_i = The value for each variable for individual postcodes

$\bar{X}_i$ = Mean for each variable for all Scottish postcode sectors

SD_i = Standard deviation for each variable for all Scottish postcode sectors

Table A.13 Calculation of deprivation score according to the Carstairs method

Case Processing Summary

		N	Percent
Cases available in analysis	Event	1545	35.5%
	Censored	2502	57.4%
	Total	4047	92.9%
Cases dropped	Cases with missing values	187	4.3%
	Cases with non-positive time	122	2.8%
	Censored cases before the earliest event in a stratum	0	.0%
	Total	309	7.1%
Total		4356	100.0%

a Dependent Variable: time elapsed from 1st RRT to listing (years)

Omnibus Tests of Model Coefficients

-2 Log Likelihood	Overall (score)			Change From Previous Step			Change From Previous Block		
	Chi-square	df	Sig.	Chi-square	df	Sig.	Chi-square	df	Sig.
22095.041	1744.002	23	.000	1674.137	23	.000	1674.137	23	.000

a Beginning Block Number 0, initial Log Likelihood function: -2 Log likelihood: 23769.178
b Beginning Block Number 1. Method = Enter

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Gender	-.179	.054	11.075	1	.001	.836	.753	.929
Age group at 1st RRT			892.620	4	.000			
35-49 yr	-.304	.069	19.194	1	.000	.738	.644	.845
50-59 yr	-.803	.073	120.495	1	.000	.448	.388	.517
60-64 yr	-1.550	.098	251.928	1	.000	.212	.175	.257
> 65 yr	-2.672	.100	720.095	1	.000	.069	.057	.084
Carstairs dep. cat.			18.479	6	.005			
Carstairs 2	-.308	.136	5.106	1	.024	.735	.562	.960
Carstairs 3	-.275	.128	4.599	1	.032	.759	.590	.977
Carstairs 4	-.373	.126	8.720	1	.003	.688	.537	.882
Carstairs 5	-.492	.135	13.376	1	.000	.611	.470	.796
Carstairs 6	-.406	.137	8.795	1	.003	.667	.510	.871
Carstairs 7	-.525	.159	10.909	1	.001	.592	.433	.808
Transplant center			174.702	3	.000			
Centre 2	-.155	.109	2.047	1	.153	.856	.692	1.059
Centre 3	-.800	.096	69.052	1	.000	.449	.372	.542
Centre 4	-.944	.084	125.113	1	.000	.389	.330	.459
Distance to Tx Centre			20.334	3	.000			
0-50 km	.124	.099	1.584	1	.208	1.132	.933	1.373
50-100 km	-.457	.118	14.956	1	.000	.633	.503	.798
>100 km	.202	.223	.820	1	.365	1.223	.791	1.892
Primary renal disease			88.026	4	.000			
Interstitial nephritis	-.206	.071	8.447	1	.004	.814	.708	.935
Multisystem disease	-.577	.085	46.608	1	.000	.561	.476	.663
Diabetes	-.650	.084	59.556	1	.000	.522	.443	.616
Other/unknown	-.453	.084	28.880	1	.000	.636	.539	.750
Type 1st RRT	.364	.054	44.853	1	.000	1.439	1.294	1.601
Year first RRT	-.051	.009	34.571	1	.000	.950	.934	.967

Table A.14 Relative risk of access to the waiting list (Cox proportional hazards model including all cases)

Case Processing Summary

		N	Percent
Cases available in analysis	Event	1015	58.4%
	Censored	638	36.7%
	Total	1653	95.2%
Cases dropped	Cases with missing values	80	4.6%
	Cases with non-positive time	2	.2%
	Censored cases before the earliest event in a stratum	1	.1%
	Total	84	4.8%
Total		1736	100.0%

a Dependent Variable: total time (days) on active wl - only time effectively on the list

Omnibus Tests of Model Coefficients

-2 Log Likelihood	Overall (score)			Change From Previous Step			Change From Previous Block		
	Chi-square	df	Sig.	Chi-square	df	Sig.	Chi-square	df	Sig.
13310.140	112.579	12	.000	116.192	12	.000	116.192	12	.000

a Beginning Block Number 0, initial Log Likelihood function: -2 Log likelihood: 13426.333
b Beginning Block Number 1. Method = Enter

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Age group at listing			47.838	4	.000			
35-49 yr	-.282	.078	12.928	1	.000	.754	.647	.880
50-59 yr	-.395	.087	20.439	1	.000	.674	.568	.800
60-64 yr	-.505	.131	14.994	1	.000	.603	.467	.779
> 65 yr	-.852	.148	33.109	1	.000	.427	.319	.570
Primary renal disease			9.583	4	.048			
Interstitial nephritis	-.115	.079	2.086	1	.149	.892	.763	1.042
Multisystem disease	-.248	.107	5.410	1	.020	.780	.633	.962
Diabetes	-.185	.108	2.897	1	.089	.831	.672	1.028
Other/unknown	-.270	.107	6.350	1	.012	.764	.619	.942
Transplant center			25.407	3	.000			
Centre 2	-.476	.133	12.818	1	.000	.621	.479	.806
Centre 3	.106	.104	1.057	1	.304	1.112	.908	1.363
Centre 4	-.145	.093	2.401	1	.121	.865	.721	1.039
Year of listing	-.044	.011	16.446	1	.000	.957	.936	.977

Table A.15 Relative risk of access to transplantation (Cox proportional hazards model including all cases)

Pro-forma for patient data collection

Fields	Criteria	Coding	Patient value
SRR number			
UKT number			
Age			
Gender	M F	1 2	
Date on W.L.	Date		
Date start RRT	Date		
Type of 1st RRT	Conservative HD APD CAPD Home-HD	0 1 2 3 4	
Length of RRT	Time		
Number of RRT switches			
Cause of renal disease	Primary Glomerulonephitis Interstitial nephropaties Multisystem disease Diabetes Unknown	1 2 3 4 5	
Date Tx	Date		
D.M. comorbid condition	No Yes	1 2	
D.M. type:	I II	1 2	
	Level of hyperglycaemia (HbA_1c)		
D.M. stages:	**No complication** **Ophtalmic complications** (retinopathy cataract) **Renal complications** (interstitial glomerulosclerosis, nephropathy) **Neurological complications** (amyotrophy, autonomic neuropathy, mononeuropathy, mononeuropathy, polyneuropathy, autonomic) **Peripheral circulatory problems** (gangrene, peripheral angiopathy, ulcer) **Arthropathy**	0 1 2 3 4 5	
Peripheral vascular disease	No Claudication Ischaemic ulcers/rest pain Revascularization (surgical/angioplasty) Amputation Venous thrombosis and embolism	1 2 3 4 5 6	
Hypertension	No Essential Secondary	1 2 3	

	Number of anti hypertensive drugs (waiting list moment)		
Ischaemic heart disease	No Abnormal ECG (otherwise unspecified) **Unstable angina** (crescendo, de novo effort, worsening effort, preinfarction syndrome, intermediate coronary syndrome) **Angina with documented spasm** (Prinzmetal, angiospastic, spasm induced, variant) Other forms of angina (**angina of effort**, stenocardia) Angina unspecified (**Ischaemic chest pain**, anginal syndrome) **MI-acute** **MI**-subsequent (**recurrent**) **MI with complications** (ASD, VSD, haemopericardium, rupture of chordae tendienae, papillary muscle, thrombosis) **Chronic ischaemic heart disease** (ATS, old MI, heart aneurisms, silent MI) Angioplasty CABG	1 2 3 4 5 6 7 8 9 10 11 12	
Valvular disease	No Yes Previous valvular surgery	1 2 3	
Pulmonary embolism	No Yes	1 2	
Arrhytmias	No Yes-no treatment Yes-Requiring treatment Yes-Pacemaker	1 2 3 4	
Heart failure	No LVF CHF	1 2 3	
Ventricular function	(Good / Mild / Moderate / Severe) Ventricular ejection fraction		
LV Hypertrophy	(Grade: Mild / Moderate / Severe) **Diagnostic modality:** **ECG = a / Echo = b**		
Other heart conditions	No Yes- (pericarditis, endocarditis, myocarditis, cardiomyopathy, conduction disorders)	1 2	
Cardiac arrest	No Yes	1 2	
	Duration		

Respiratory problems	No Asthma COAD Emphysema Bronchitis Bronchiectasis Other (pneumoconiosis of various origin, TB) Respiratory failure Other (pleural effusion, pleural plaque, lung abscess)	1 2 3 4 5 6 7 8 9	
	FEV1/FVC		
Cerebro-vascular disease	No Other (stenosis of cerebral, carotid arteries, aneurysms) TIA CVA (documented) Hypertensive encephalopathy Fits	1 2 3 4 5 6	
Liver disease abnormal LFT's:	No Yes	1 2	
Serum albumin	> 3g/dL >2.5 to < 3g/dL <2.5g/dL	1 2 3	
Biopsy proven hepatic dysfuction	No Yes	1 2	
Hepatitis	No HbsAg +ve HbcAb +ve Hep C +ve	1 2 3 4	
ALD	No Yes	1 2	
Other (portal hyper ertension, fatty liver)	No Yes	1 2	
Ascites	No Yes	1 2	
Cirrhosis	No Yes	1 2	
Malignancy other than BCC	No Primary Metastatic	1 2 3	
Malignancy stage	I II III IV	1 2 3 4	
Anaemia	No Yes	1 2	
Other viral infections	No CMV EBV	1 2 3	
HIV	No Yes	1 2	
Warfarin	No Yes – for IHD Yes – for vascular access	1 2 3	

Smoker	No Active Ex-smoker Number of cigs/day		1 2 3	
Nutrition	BMI			
	Cachectic Obese		1 2	
Inability to ambulate	No Yes		1 2	
GI disorders	Duodenal ulcer / Surgery Gastric ulcer / Surgery Gallstones / Cholecystectomy GI bleed Dyspesia/Hiatus hernia/GORD			
Urological pathology	TURP Ileal conduit Congenital abnormalities Neurogenic bladder Nephrectomy			
Hyperparathyroidism	No Yes Previous parathyroidecttomy		1 2 3	
Other pathology not identified above				
Blood group and HLA	Blood group A B DR Lymphocytotoxic Ab level Mismatch tier (1, 2, 3)			
Biochemistry results	Date: Ureea = Creatinine = Na = K = CO2 = Bilirubin = ALT =	 A.P. = GGT = Albumin = Calcium = Phosphate = PTH = Cholesterol =	Date: Hb = Hct = MCV = MCH = PLT =	 WBC = N = L = M = E = B =
Donor data	Type Age CMV status Cause of death Cold ischaemic time Mismatch Blood group and Rh			
Rejection episodes	Date Biopsy Grade Treatment Outcome			
DGF	Date Duration			
Immunosuppression	Prednisolone Tacrolimus Rapamycin Other		Cyclosporine MMF Antibodies	

Case Processing Summary

		N	Percent
Cases available in analysis	Event[a]	281	16.2%
	Censored	1287	74.1%
	Total	1568	90.3%
Cases dropped	Cases with missing values	76	4.4%
	Cases with non-positive time	50	2.9%
	Censored cases before the earliest event in a stratum	42	2.4%
	Total	169	9.7%
Total		1736	100.0%

a Dependent Variable: survival from wl for patients on dialysis censored for tx

Omnibus Tests of Model Coefficients[a,b]

-2 Log Likelihood	Overall (score)			Change From Previous Step			Change From Previous Block		
	Chi-square	df	Sig.	Chi-square	df	Sig.	Chi-square	df	Sig.
3214.975	214.154	18	.000	202.907	18	.000	202.907	18	.000

a Beginning Block Number 0, initial Log Likelihood function: -2 Log likelihood: 3417.882
b Beginning Block Number 1. Method = Enter

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Gender	-.090	.127	.510	1	.475	.913	.713	1.171
Primary renal disease			82.033	4	.000			
Interstitial nephritis	-.253	.209	1.470	1	.225	.776	.515	1.169
Multisystem disease	.131	.214	.373	1	.541	1.139	.750	1.732
Diabetes	1.239	.186	44.419	1	.000	3.454	2.399	4.973
Other/unknown	.301	.206	2.140	1	.144	1.352	.903	2.024
Type 1st RRT	.162	.129	1.570	1	.210	1.176	.913	1.514
Age group at listing			66.154	4	.000			
35-49 yr	1.009	.282	12.815	1	.000	2.743	1.579	4.767
50-59 yr	1.508	.273	30.587	1	.000	4.518	2.648	7.710
60-64 yr	1.705	.298	32.820	1	.000	5.500	3.069	9.854
> 65 yr	2.027	.283	51.177	1	.000	7.588	4.355	13.221
1st RRT-listing time (year)	.304	.067	20.783	1	.000	1.355	1.189	1.544
Carstairs dep. cat.			4.445	6	.617			
Carstairs 2	-.288	.297	.941	1	.332	.750	.419	1.342
Carstairs 3	-.297	.274	1.173	1	.279	.743	.435	1.271
Carstairs 4	-.221	.272	.662	1	.416	.802	.471	1.365
Carstairs 5	-.140	.291	.232	1	.630	.869	.492	1.537
Carstairs 6	.076	.289	.069	1	.793	1.079	.612	1.902
Carstairs 7	-.338	.416	.662	1	.416	.713	.316	1.611
Distance to Tx center (km)	.000	.001	.115	1	.735	1.000	.998	1.003

Table A.16 Cox model for risk of death on dialysis on the waiting list (unadjusted for comorbidity).

Cases available in analysis	Event[a]	115	6.6%
	Censored	663	38.2%
	Total	778	44.8%
Cases dropped	Cases with missing values	909	52.4%
	Cases with non-positive time	25	1.4%
	Censored cases before the earliest event in a stratum	24	1.4%
	Total	959	55.2%
Total		1736	100.0%

a Dependent Variable: survival from wl for patients on dialysis censored for tx

Omnibus Tests of Model Coefficients[a,b]

-2 Log Likelihood	Overall (score)			Change From Previous Step			Change From Previous Block		
	Chi-square	df	Sig.	Chi-square	df	Sig.	Chi-square	df	Sig.
1059.901	178.595	32	.000	146.883	32	.000	146.883	32	.000

a Beginning Block Number 0, initial Log Likelihood function: -2 Log likelihood: 1206.784

b Beginning Block Number 1. Method = Enter

Variables in the equation	B	SE	Wald	Df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Gender	.130	.225	.335	1	.563	1.139	.733	1.770
Primary renal disease			18.729	4	.001			
Interstitial nephritis	-.386	.354	1.187	1	.276	.680	.339	1.361
Multisystem disease	.197	.340	.336	1	.562	1.218	.625	2.372
Diabetes	1.050	.354	8.796	1	.003	2.856	1.428	5.716
Other/unknown	-.045	.380	.014	1	.906	.956	.454	2.013
Type 1st RRT	-.022	.230	.009	1	.923	.978	.624	1.534
Age group at listing			20.413	4	.000			
35-49 yr	.396	.473	.699	1	.403	1.485	.588	3.754
50-59 yr	1.003	.472	4.517	1	.034	2.726	1.081	6.873
60-64 yr	1.118	.525	4.535	1	.033	3.058	1.093	8.557
> 65 yr	1.622	.476	11.613	1	.001	5.064	1.992	12.874
1st RRT-listing time (year)	-.050	.148	.113	1	.736	.951	.712	1.271
Carstairs dep. cat.			10.414	6	.108			
Carstairs 2	-.890	.435	4.178	1	.041	.411	.175	.964
Carstairs 3	-.148	.414	.127	1	.721	.863	.383	1.942
Carstairs 4	-.523	.400	1.708	1	.191	.593	.270	1.299
Carstairs 5	-.480	.481	.996	1	.318	.619	.241	1.589
Carstairs 6	.253	.439	.332	1	.564	1.288	.544	3.049
Carstairs 7	-.276	.639	.186	1	.666	.759	.217	2.656
Distance to Tx center (km)	.000	.002	.015	1	.904	1.000	.996	1.004
PVD	.315	.261	1.447	1	.229	1.370	.820	2.286
Hypertension	.196	.352	.312	1	.576	1.217	.611	2.425
IHD	.623	.241	6.699	1	.010	1.864	1.163	2.988
Valvular disease	.673	.285	5.582	1	.018	1.960	1.122	3.427
Arrhythmias	.507	.306	2.746	1	.098	1.660	.911	3.025
Heart failure	.320	.329	.948	1	.330	1.377	.723	2.621
LVH	-.593	.223	7.061	1	.008	.553	.357	.856
Respiratory disease	.787	.252	9.759	1	.002	2.197	1.341	3.600
CVD	.898	.276	10.603	1	.001	2.455	1.430	4.215
Neoplasia	.942	.669	1.984	1	.159	2.564	.692	9.507
GI Disorders	.290	.224	1.669	1	.196	1.336	.861	2.074
Urological disorders	-.157	.334	.220	1	.639	.855	.444	1.647
Hyperlipidaemia	.195	.328	.354	1	.552	1.216	.639	2.314
BMI	-.019	.020	.928	1	.335	.981	.943	1.020

Table A.17 Cox model for risk of death on dialysis on the waiting list (adjusted for comorbidity)

Case Processing Summary

		N	Percent
Cases available in analysis	Event[a]	181	16.5%
	Censored	845	77.2%
	Total	1026	93.7%
Cases dropped	Cases with missing values	61	5.6%
	Cases with non-positive time	8	.7%
	Censored cases before the earliest event in a stratum	0	.0%
	Total	69	6.3%
Total		1095	100.0%

a Dependent Variable: survival for transplanted patients (years)

Omnibus Tests of Model Coefficients[a,b]

-2 Log Likelihood	Overall (score)			Change From Previous Step			Change From Previous Block		
	Chi-square	df	Sig.	Chi-square	df	Sig.	Chi-square	df	Sig.
2130.561	135.074	19	.000	121.989	19	.000	121.989	19	.000

a Beginning Block Number 0, initial Log Likelihood function: -2 Log likelihood: 2252.550

b Beginning Block Number 1. Method = Enter

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Gender	-.027	.164	.028	1	.868	.973	.705	1.343
Primary renal disease			27.115	4	.000			
Interstitial nephritis	-.057	.215	.070	1	.792	.945	.620	1.441
Multisystem disease	.078	.247	.099	1	.753	1.081	.666	1.756
Diabetes	.971	.223	18.934	1	.000	2.642	1.705	4.091
Other/unknown	.130	.276	.223	1	.637	1.139	.663	1.956
Type 1st RRT	.353	.156	5.133	1	.023	1.424	1.049	1.932
Age group at transplantation			75.923	4	.000			
35-49 yr	.834	.271	9.454	1	.002	2.303	1.353	3.919
50-59 yr	1.520	.264	33.252	1	.000	4.573	2.728	7.666
60-64 yr	2.101	.303	48.089	1	.000	8.172	4.513	14.797
> 65 yr	2.161	.304	50.386	1	.000	8.679	4.779	15.761
Carstairs dep. cat.			5.471	6	.485			
Carstairs 2	.015	.408	.001	1	.970	1.015	.457	2.258
Carstairs 3	-.145	.399	.131	1	.717	.865	.396	1.893
Carstairs 4	.299	.382	.616	1	.433	1.349	.639	2.850
Carstairs 5	.001	.418	.000	1	.999	1.001	.441	2.269
Carstairs 6	.278	.417	.444	1	.505	1.320	.583	2.988
Carstairs 7	.183	.524	.122	1	.727	1.201	.430	3.357
Distance to Tx center (km)	.004	.001	5.561	1	.018	1.004	1.001	1.006
1st RRT-listing time (year)	.071	.102	.488	1	.485	1.074	.880	1.311
Listing-transplant time (year)	.000	.000	.608	1	.436	1.000	.999	1.000

Table A.18 Cox model for risk of death following transplantation (unadjusted for comorbidity)

Cases available in analysis	Event[a]	80	7.3%
	Censored	482	44.0%
	Total	562	51.3%
Cases dropped	Cases with missing values	530	48.4%
	Cases with non-positive time	2	.2%
	Censored cases before any event	1	.1%
Total		1095	100.0%

a Dependent Variable: survival for transplanted patients (years)

Omnibus Tests of Model Coefficients[a,b]

-2 Log Likelihood	Overall (score)			Change From Previous Step			Change From Previous Block		
	$\chi 2$	df	Sig.	$\chi 2$	df	Sig.	$\pm\chi 2$	df	Sig.
804.252	103.841	33	.000	90.403	33	.000	90.403	33	.000

Beginning Block Number 0, initial Log Likelihood function: -2 Log likelihood: 894.655

b Beginning Block Number 1. Method = Enter

Variables in the equation	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Gender	.124	.274	.204	1	.651	1.132	.662	1.935
Primary renal disease			15.328	4	.004			
Interstitial nephritis	.062	.360	.030	1	.862	1.064	.525	2.157
Multisystem disease	.198	.399	.247	1	.619	1.219	.558	2.664
Diabetes	1.161	.366	10.089	1	.001	3.194	1.560	6.539
Other/unknown	-.357	.592	.364	1	.546	.700	.219	2.233
Type 1st RRT	.059	.256	.053	1	.817	1.061	.642	1.753
Age group at transplantation			21.616	4	.000			
35-49 yr	1.398	.514	7.414	1	.006	4.048	1.480	11.074
50-59 yr	1.890	.522	13.122	1	.000	6.622	2.381	18.417
60-64 yr	1.780	.641	7.717	1	.005	5.927	1.689	20.802
> 65 yr	2.617	.581	20.282	1	.000	13.700	4.385	42.797
Carstairs dep. cat.			4.503	6	.609			
Carstairs 2	1.244	1.055	1.393	1	.238	3.471	.439	27.421
Carstairs 3	.954	1.067	.799	1	.371	2.596	.321	21.026
Carstairs 4	1.427	1.053	1.837	1	.175	4.165	.529	32.787
Carstairs 5	.814	1.089	.559	1	.455	2.257	.267	19.076
Carstairs 6	1.382	1.074	1.657	1	.198	3.983	.486	32.670
Carstairs 7	1.115	1.152	.937	1	.333	3.051	.319	29.189
Distance to Tx center (km)	.001	.003	.074	1	.785	1.001	.994	1.008
1st RRT-listing time (year)	.104	.178	.341	1	.559	1.110	.782	1.574
Listing-transplant time (year)	.000	.000	.535	1	.464	1.000	.999	1.000
PVD	.199	.336	.351	1	.554	1.220	.632	2.355
Hypertension	.665	.513	1.682	1	.195	1.945	.712	5.316
IHD	-.147	.332	.196	1	.658	.863	.450	1.656
Valvular disease	.288	.402	.513	1	.474	1.334	.606	2.933
Arrhythmias	.473	.650	.529	1	.467	1.604	.449	5.734
Heart failure	-.002	.537	.000	1	.997	.998	.348	2.860
LVH	.254	.297	.734	1	.391	1.290	.721	2.308
Respiratory disease	.068	.368	.034	1	.853	1.070	.521	2.200
CVD	.584	.423	1.899	1	.168	1.792	.782	4.111
Neoplasia	1.100	.558	3.894	1	.048	3.005	1.008	8.962
GI disorders	.571	.280	4.153	1	.042	1.771	1.022	3.067
Urological disorders	.037	.366	.010	1	.919	1.038	.507	2.126
Hyperlipidaemia	.016	.462	.001	1	.973	1.016	.410	2.514
BMI	-.054	.028	3.642	1	.056	.947	.896	1.001

Table A.19 Cox model for risk of death following transplantation (adjusted for comorbidity)

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	2288.729	2018.118
AIC	2288.729	2060.118
SBC	2288.729	2127.859

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	270.6110	21	<.0001
Score	356.4909	21	<.0001
Wald	262.6021	21	<.0001

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Variable	Parameter DF	Standard Estimate	Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
35-49 yr	1	0.80557	0.32585	6.1118	0.0134	2.238	1.182	4.239
50-59 yr	1	1.52512	0.32645	21.8258	<.0001	4.596	2.424	8.714
60-64 yr	1	1.60521	0.36214	19.6473	<.0001	4.979	2.448	10.125
> 65 yr	1	2.35622	0.33648	49.0349	<.0001	10.551	5.456	20.404
Gender	1	0.26698	0.16618	2.5812	0.1081	1.306	0.943	1.809
Centre 2	1	0.82691	0.18887	19.1687	<.0001	2.286	1.579	3.310
Centre 3	1	-0.41083	0.21600	3.6177	0.0572	0.663	0.434	1.013
Diabetes	1	0.97042	0.17876	29.4688	<.0001	2.639	1.859	3.746
Hypertension	1	0.41558	0.25289	2.7006	0.1003	1.515	0.923	2.487
IHD	1	0.34544	0.17266	4.0028	0.0454	1.413	1.007	1.981
Valvular dis.	1	0.48764	0.20278	5.7833	0.0162	1.628	1.094	2.423
PE	1	-0.72978	0.49491	2.1743	0.1403	0.482	0.183	1.272
Arrhythmias	1	0.38298	0.24691	2.4059	0.1209	1.467	0.904	2.380
Other heart dis	1	0.59693	0.26498	5.0748	0.0243	1.817	1.081	3.053
Respiratory dis	1	0.44432	0.19947	4.9618	0.0259	1.559	1.055	2.305
CVD	1	0.39571	0.21599	3.3564	0.0669	1.485	0.973	2.268
Neoplasia	1	0.73939	0.37079	3.9764	0.0461	2.095	1.013	4.332
GI disorders	1	0.22040	0.17372	1.6096	0.2045	1.247	0.887	1.752
smoker	1	0.31094	0.16578	3.5178	0.0607	1.365	0.986	1.889
Malnourished	1	0.54074	0.26620	4.1262	0.0422	1.717	1.019	2.894
Blood gr.A	1	-0.23385	0.16727	1.9544	0.1621	0.791	0.570	1.099

Figure A.4.1 Summary of the baseline Cox regression analysis used to determine the factors for the survival predictive model.

Average treatment

Total	Event	Censored	Percent Censored
874	193	681	77.92

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	2394.628	2113.209
AIC	2394.628	2155.209
SBC	2394.628	2223.726

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	281.4191	21	<.0001
Score	374.1650	21	<.0001
Wald	276.0495	21	<.0001

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
35-49 yr	1	0.75389	0.31449	5.7465	0.0165	2.125
50-59 yr	1	1.46363	0.31181	22.0336	<.0001	4.322
60-64 yr	1	1.54045	0.35305	19.0384	<.0001	4.667
> 65 yr	1	2.32296	0.32494	51.1064	<.0001	10.206
Gender	1	0.24861	0.16341	2.3147	0.1282	1.282
Transplant center 2	1	0.82955	0.18309	20.5294	<.0001	2.292
Transplant center 3	1	-0.44666	0.21209	4.4353	0.0352	0.640
Diabetes	1	0.97736	0.17634	30.7206	<.0001	2.657
Ischaemic heart dis	1	0.34356	0.17068	4.0514	0.0441	1.410
Valvular disease	1	0.48013	0.20196	5.6519	0.0174	1.616
Pulmonary embolism	1	-0.76258	0.49251	2.3974	0.1215	0.466
Arrhythmias	1	0.38039	0.24572	2.3965	0.1216	1.463
CVD	1	0.41491	0.21153	3.8473	0.0498	1.514
Hypertension	1	0.42601	0.24624	2.9933	0.0836	1.531
Respiratory disease	1	0.46732	0.19445	5.7756	0.0162	1.596
Other heart dis	1	0.58845	0.26466	4.9437	0.0262	1.801
GI disorders	1	0.22936	0.16879	1.8465	0.1742	1.258
Neoplasia	1	0.73981	0.37011	3.9955	0.0456	2.096
Smoker	1	0.29710	0.16254	3.3410	0.0676	1.346
Malnourished	1	0.53309	0.24739	4.6433	0.0312	1.704
Blood group A	1	-0.26312	0.16448	2.5590	0.1097	0.769

Figure A.4.2 Summary of the Cox regression analysis for the survival under "average treatment" scenario

No transplant - censored at time of transplant

Total	Event	Censored	Percent Censored
878	116	762	86.79

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	1209.836	1042.683
AIC	1209.836	1084.683
SBC	1209.836	1142.509

Testing Global Null Hypothesis: BETA=0

Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	167.1527	21	<.0001
Score	208.9190	21	<.0001
Wald	153.2053	21	<.0001

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
35-49 yr	1	-0.01494	0.45914	0.0011	0.9740	0.985
50-59 yr	1	1.00082	0.43467	5.3014	0.0213	2.721
60-64 yr	1	0.91014	0.50215	3.2851	0.0699	2.485
>65 yr	1	1.27792	0.46122	7.6769	0.0056	3.589
Gender	1	0.00564	0.22740	0.0006	0.9802	1.006
Transplant center 2	1	0.64872	0.24285	7.1354	0.0076	1.913
Transplant center 3	1	-1.09392	0.32479	11.3441	0.0008	0.335
Diabetes	1	1.35650	0.24383	30.9509	<.0001	3.883
Ischaemic heart dis	1	0.38346	0.23509	2.6606	0.1029	1.467
Valvular disease	1	0.66919	0.25960	6.6446	0.0099	1.953
Pulmonary embolism	1	-0.36521	0.65094	0.3148	0.5748	0.694
Arrhythmias	1	0.08141	0.29415	0.0766	0.7820	1.085
CVD	1	0.78555	0.25841	9.2412	0.0024	2.194
Hypertension	1	0.11743	0.32134	0.1336	0.7148	1.125
Respiratory disease	1	0.50438	0.24747	4.1541	0.0415	1.656
Other heart dis.	1	0.44600	0.36195	1.5184	0.2179	1.562
GI disorders	1	0.17034	0.22191	0.5892	0.4427	1.186
Neoplasia	1	0.49526	0.61722	0.6438	0.4223	1.641
Smoker	1	-0.09141	0.23068	0.1570	0.6919	0.913
Malnourished	1	0.36899	0.32737	1.2704	0.2597	1.446
Blood group A	1	-0.01486	0.23133	0.0041	0.9488	0.985

Figure A.4.3 Summary of the Cox regression analysis for the survival under "no transplant" scenario

Following transplant

Total	Event	Censored	Percent Censored
611	77	534	87.40

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	877.677	774.147
AIC	877.677	816.147
SBC	877.677	865.367

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	103.5300	21	<.0001
Score	130.1759	21	<.0001
Wald	98.7582	21	<.0001

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
35-49 yr	1	1.13495	0.44764	6.4284	0.0112	3.111
50-59 yr	1	1.58291	0.46686	11.4957	0.0007	4.869
60-64 yr	1	1.99169	0.53637	13.7883	0.0002	7.328
>65 yr	1	2.75975	0.50158	30.2733	<.0001	15.796
Gender	1	0.39573	0.26001	2.3164	0.1280	1.485
Transplant center 2	1	1.04668	0.32380	10.4492	0.0012	2.848
Transplant center 3	1	-0.04090	0.30721	0.0177	0.8941	0.960
Diabetes	1	0.91256	0.30386	9.0193	0.0027	2.491
Ischaemic heart dis	1	-0.04642	0.32479	0.0204	0.8863	0.955
Valvular disease	1	0.43998	0.37566	1.3718	0.2415	1.553
Pulmonary embolism	1	-0.86400	0.81627	1.1204	0.2898	0.421
Arrhythmias	1	0.14464	0.63641	0.0517	0.8202	1.156
CVD	1	0.15750	0.41756	0.1423	0.7060	1.171
Hypertension	1	0.67537	0.45263	2.2264	0.1357	1.965
Respiratory disease	1	0.34763	0.35722	0.9470	0.3305	1.416
Other heart disease	1	0.52389	0.46152	1.2886	0.2563	1.689
GI disorders	1	0.31930	0.29287	1.1886	0.2756	1.376
Neoplasia	1	1.20736	0.49958	5.8407	0.0157	3.345
Smoker	1	0.69125	0.24968	7.6648	0.0056	1.996
Malnourished	1	0.73837	0.39202	3.5475	0.0596	2.093
Blood group A	1	-0.17645	0.25932	0.4629	0.4962	0.838

Figure A.4.4 Summary of the Cox regression analysis for the survival under "post-transplant" scenario

PUBLICATIONS:

1. Does a kidney sharing alliance have to sacrifice cold ischaemic time for better HLA matching?
   G.C. Oniscu, W. Plant, P. Pocock, J.L.R. Forsythe
   Transplantation, 2002; 73: 1647-1652

2. Transplantation versus dialysis in patients over 60 years old
   G.C. Oniscu, A. Schalkwijk, J.L.R. Forsythe
   J Am Soc Nephrol 2001; 12: 909A

3. Factors influencing the access to renal transplant waiting list and renal transplantation
   G.C. Oniscu, K. Simpson, A. Schalkwijk, H. Short, J.L.R. Forsythe
   J Am Soc Nephrol 2001; 12: 909A

4. The relationship between comorbidity, socio-demographic factors and speed of access to the renal transplant waiting list and renal transplantation in Scotland
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   Transplantation, 2002; 74 (S4): 363

5. Comparison of mortality in patients listed for renal transplantation: reduced risk for transplantation vs. dialysis
   G.C. Oniscu, H. Brown, J.L.R. Forsythe
   Transplantation, 2002; 74 (S4): 451

PRESENTATIONS:

1. Equity of access to renal transplant waiting list and renal transplantation in Scotland
   Medawar Prize Session, British Transplantation Society, Oxford, March 2001

2. Is it worth forming a waiting list alliance? Figures from Scotland-Northern Ireland Alliance for three years
   British Transplantation Society, Oxford, March 2001

3. Equity of access to renal transplant waiting list and renal transplantation in Scotland
   Awarded the Chiene Medal,
   School of Surgery Day, Edinburgh, November 2001

4. How old is old for transplantation
   British Transplant Society Congress, Cambridge, 2002

5. Comparison of mortality in patients listed for renal transplantation: Reduced risk for transplantation versus dialysis
   British Transplant Society Congress, Cambridge, 2002

6. How great is the survival advantage of transplantation over dialysis on elderly patients
   Association of Surgeons of Great Britain and Ireland, Dublin, 2002

7. Advantages and disadvantages of a wider regional kidney sharing alliance
   10th Congress of the European Society for Transplantation, Lisbon 2001

8. Factors influencing the access to renal transplant waiting list and renal transplantation
   10th Congress of the European Society for Transplantation, Lisbon 2001

9. Transplantation versus dialysis in patients over 60 years old (poster)
   ASN/ISN World Congress of Nephrology, San Francisco, 2001

10. Factors influencing the access to renal transplant waiting list and renal transplantation (poster)
    ASN/ISN World Congress of Nephrology, San Francisco, 2001

11. Impact of gender on access to the renal transplant waiting list and 1st renal transplant for adult patients
    American Transplant Congress, Washington, 2002

12. How great is the survival advantage of transplantation over dialysis on elderly patients
    American Transplant Congress, Washington, 2002

13. How old is old for transplantation
    American Transplant Congress, Washington, 2002

14. The relationship between comorbidity, socio-demographic factors and speed of access to the renal transplant waiting list and renal transplantation in Scotland
    International Congress of The Transplantation Society, Miami, 2002

15. Comparison of mortality in patients listed for renal transplantation: reduced risk for transplantation vs. dialysis
    International Congress of The Transplantation Society, Miami, 2002

16. Survival advantage for transplantation compared with dialysis. A practical application
    School of Surgery Day, Edinburgh, November 2002